UNIVERSITY OF ALBERTA

Radical Aryl Transfer, and Synthetic Studies Related to Halichlorine

by

Shunzhen Kang ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

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DEGREE: Doctor of Philosophy

YEAR THIS DEGREE GRANTED: 2002

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Radical Aryl Transfer, and Synthetic Studies Related to Halichlorine** submitted by **Shunzhen Kang** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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To my family

ABSTRACT

The first Chapter of this thesis describes a study of radical aryl transfer based on halophosphinates. Such transfer from phosphorus to carbon had not been observed before. The results show that phosphinates can be used for the preparation of biaryls by intramolecular radical aryl transfer. A number of examples has been studied, and the generality of the process, as well as part of the mechanism, has been established. The method extends the range of available linkers between aryl groups that are to be joined by intramolecular *ipso* radical transfer, and the results of this work have been published (*J. Org. Chem.* **2001**, *66*, 6083).

The second Chapter of this thesis describes synthetic studies on halichlorine. Halichlorine is a novel alkaloid, which was recently isolated from a marine organism. Its biological properties may establish it as an important lead compound for the design of anti-inflammatory drugs. The 6-azaspiro[4,5]decane core is the most conspicuous feature in halichlorine, in which three stereogenic centers [C(9), C(13), C(14)] are contiguous. Several synthetic routes have been explored, and the work was taken as far as the amine **63.3**. Further studies on the elaboration of this compound are being pursued in this laboratory.

ACKNOWLEDGMENTS

I would like to express my gratitude to Dr. D. L. J. Clive for his constant support and encouragement during the course of my Ph.D. program, and for his assistance during the preparation of this thesis.

Thanks also go to a number of other people:

- my friends and co-workers, both in Dr. Clive's group and other groups, for many helpful discussions about chemistry and life. I especially would like to thank my laboratory colleagues, past and present, for their valuable help and advice during the initial stages of my laboratory work and for creating a stimulating scientific environment.
- the staff of the IR, MS, NMR and elemental analysis labs, for sharing their knowledge and for their helpful advice.
- the chemical, glass, machine and electronic shop staff
- the staff in the General Office, for their help with administrative duties.
- Dr. Norman Gee, for his help with my undergraduate laboratory teaching.

Finally, I would like to thank my family for their support and encouragement.

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List of abbreviations

Ac.....acetyl

AIBN.....2,2'-azobisisobutyronitrile

Ar.....aryl

9-BBN.....9-borabicyclo[3,3,1]nonane

Bn.....benzyl

Boc.....*tert*-butoxycarbonyl

Bu.....butyl

t-Bu.....*tert*-butyl

calcd.....calculated

Cbz.....benzyloxycarbonyl

DCC.....*N,N*-dicyclohexylcarbodiimide

DBU.....1,8-diazabicyclo[5.4.0]undec-7-ene

DIBAL-H.....diisobutylaluminum hydride

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMPU.....1,3-dimethyl-3,4,5,6-tetrahydro-2(1 H)-pyrimidinone

DMSO.....dimethyl sulfoxide

DPPA.....diphenylphosphoryl azide

EDCI.....*N*-(3-dimethylamino)propyl-*N*-ethylcarbodiimde

Et.....ethyl

G-COSY.....gradient correlation spectroscopy

HMBC.....^{1}H-detected multiple-bond heteronuclear multiple-quantum coherence

HMQC.....^{1}H-detected heteronuclear multiple-quantum

coherence

Hz.....hertz

KHMDS.....potassium hexamethyldisilazane

LAH.....lithium aluminum hydride

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazane

Me.....methyl

Mes.....mesityl, 2,4,6-trimethylphenyl

mp.....melting point

Ms.....methanesulfonyl

MS.....mass spectrometry

NaHMDS.....sodium hexamethyldisilazane

NBS.....*N*-bromosuccinimide

NMO.....4-methylmorpholine *N*-oxide

NMR.....nuclear magnetic resonance

NOE.....nuclear Overhauser enhancement

PCC.....pyridinium chlorochromate

PDC.....pyridinium dichromate

Pg.....protecting group

Ph.....phenyl

Piv.....trimethylacetyl (pivaloyl)

Pmb.....*p*-methoxybenzyl

PMP.....*p*-methoxyphenyl

Pr.....propyl

i-Pr.....isopropyl

Py.....pyridine

rt.....room temperature

TBAF.....tetrabutylammonium fluoride

TBDPS.....*tert*-butyldiphenylsilyl

TBDMS.....*tert*-butyldimethylsilyl

TES.....triethylsilyl

TIPS.....triisopropylsilyl

TMS.....trimethylsilyl

Tf.....trifluoromethanesulfonyl

TFA.....trifluoroacetic acid

THF.....tetrahydrofuran

TLC.....thin layer chromatography

TPAP.....tetra-*n*-propylammonium perruthenate

T-ROESY.....transmitter rotating frame nuclear Overhauser and exchange spectroscopy

Ts.....*p*-toluenesulfonyl

Chapter 1

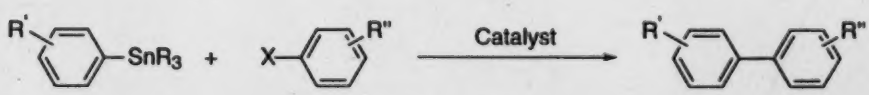
Synthesis of biaryls by intramolecular radical transfer in phosphinates

Introduction

Biaryls and their derivatives are an important class of organic compounds; the biaryl unit is represented in several types of compounds of current interest, including natural products, polymers, liquid crystals, ligands of asymmetric catalysts and molecules of medicinal interest,[1] and both natural and unnatural biaryls constitute attractive synthetic targets. A number of catalytic methods[2] for forming these molecules from two monoaryl precursors in a cross-coupling reaction have been developed over the last two decades. The most commonly used catalytic methods in biaryl synthesis are the Stille and Suzuki couplings.[3]

In the late 1970's the Stille reaction started to be applied to biaryl synthesis. The reaction uses aryl stannanes **1.1** (Ar^1SnR_3, R = Me, Bu) and aryl halides or triflates **1.2** (Ar^2X, X = halogen or triflate) as the coupling partners (Scheme 1). The reaction is extremely versatile, as it proceeds under neutral conditions and can tolerate a wide range of substituents on both coupling partners.

Scheme 1

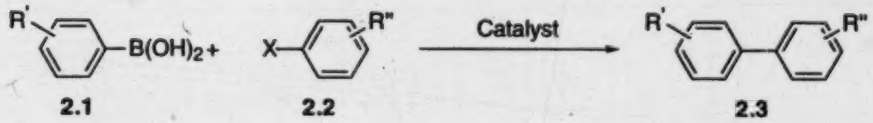


1.1 **1.2** **1.3**

The early 1980's saw the advent of the Suzuki coupling, which, like the Stille coupling, has proved extremely

versatile and has found extensive use in natural product synthesis. Boronic acids **2.1** [$Ar^1B(OH)_2$] are the usual substrates in this reaction together with aryl halides or triflates **2.2** (Ar^2X, X = halogen or triflate), although esters of boronic acids and arylboranes are frequently used (Scheme 2).

Scheme 2



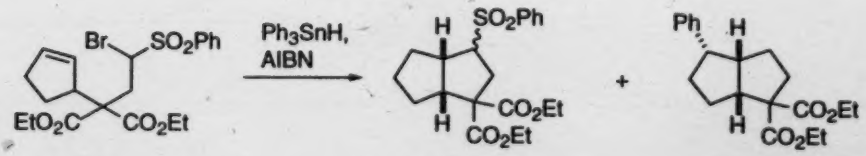
2.1 **2.2** **2.3**

The available catalysts used in the above organometallic routes are often not compatible with functionality present on the coupling partners, are difficult to prepare, or are air or moisture sensitive, and few can be purified and stored. In addition, problems may still arise when sterically congested products are required.

Radical aryl transfer, even though it involves using toxic tin reagents, might overcome some of these disadvantages for making biaryls.

The first instance of a radical aryl transfer observed

Scheme 3

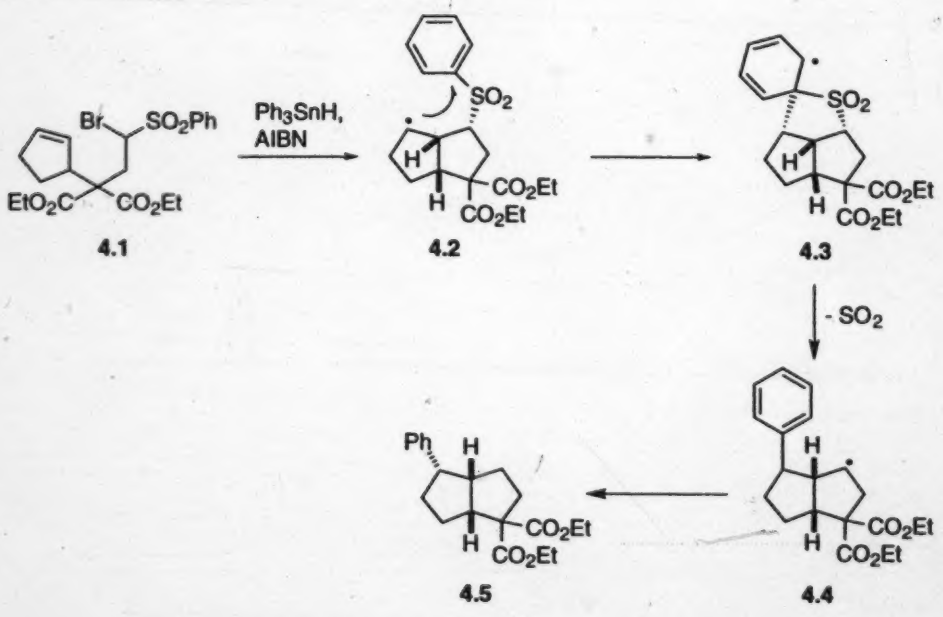


3.1 **3.2** **3.3**

in this laboratory was met during the cyclization of **3.1** to **3.2**.[4] One of the byproducts (18%) was compound **3.3** (Scheme 3). This must have been formed by an intramolecular *ipso* attack (Scheme 4) and subsequent loss of SO_2.

At that time, a number of radical aryl transfers were already known, and more have since been reported. The transfers involve migration of the aryl group (or, in a few cases, of a vinyl unit, ArC=C) from carbon to carbon,[5] from carbon to silicon,[6] from carbon to oxygen,[7] or from a heteroatom to carbon: O→C,[8] N→C,[9] Si→C,[10] S(VI)→C,[4,11] or Sn→C.[12] Where the initial radical is carbon-centered, it can be a vinyl,[11g,h] aryl,[5f,g,k,8e,f,9a,b,10f,11f,i,j,k,m] or an alkyl radical.[4,5a-e,h-j,8a-d,9,10a-e,11a-e,1,12] In the latter case, it

Scheme 4

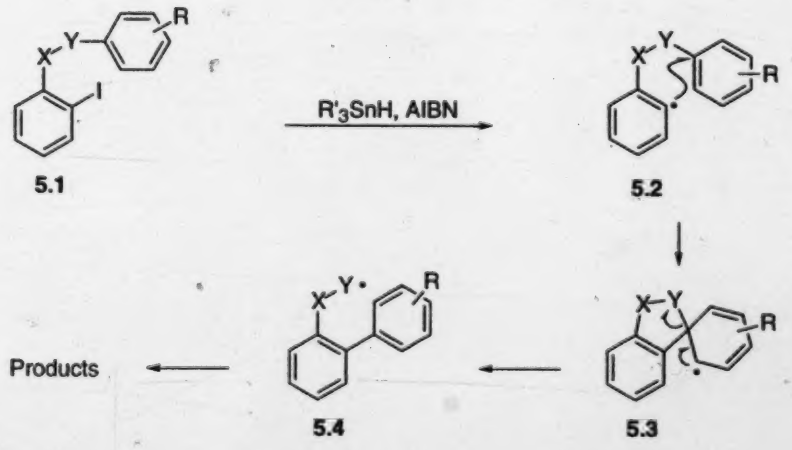


4.1 **4.2** **4.3** **4.4** **4.5**

can even be stabilized by a heteroatom,[8a] or be adjacent to an electron-withdrawing group[5e,h] or an aromatic ring,[8b] and still engage in satisfactory transfer.

The transfer of aryl groups involves *ipso* attack of a radical on the aromatic ring, and transition state ring sizes for the intermediate cyclization adduct (see **5.3**, Scheme 5) are usually 5- or 6-membered (X-Y represents a chain of 2 or 3 atoms). If the transfer involves generation of a new stereogenic center, then in some cases the process is stereoselective, either by reason of enforced delivery across one face of a cyclic structure,[4,8d] or because the chain connecting the initial radical with the acceptor aryl group adopts a chair transition state,[10d,e,11l] or otherwise avoids unfavorable nonbonded interactions.[5j,11e] Much of the published work has involved tethering two units – the radical center and the aryl acceptor – by means of an SO_2-containing

Scheme 5

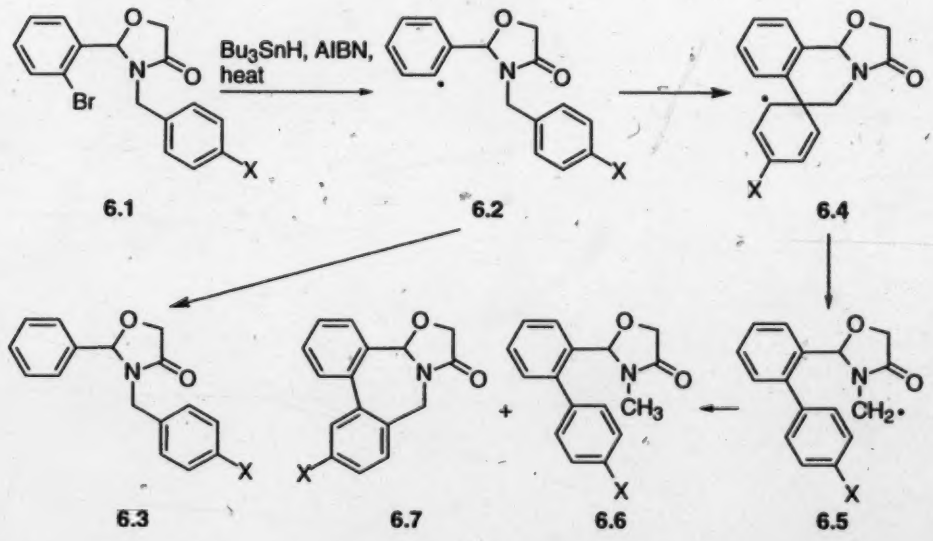


linkage.[4,11a-m] Some of the aryl transfers generate biaryls,[5f,g,k,8e,f,9a,b,10f,11f,i,j,m] and some of the reports describe the preparation of quite hindered biaryls.[5g,11i,m]

Radical aryl transfer from carbon to carbon

The first attempt, to my knowledge, to develop an *ipso*-substitution involving migration of an aryl group from an alkyl group (amidomethyl group) was reported by Renaud.[5f] The critical step of this free radical approach to *ortho*-aryl benzaldehyde derivatives is the radical addition at the hindered *ipso*-position. To force the system to react at this position, an intramolecular version based on a 6-*exo*-cyclization, using a glycolamide template was developed (Scheme 6). The well-documented stability of 1-amidoalkyl

Scheme 6



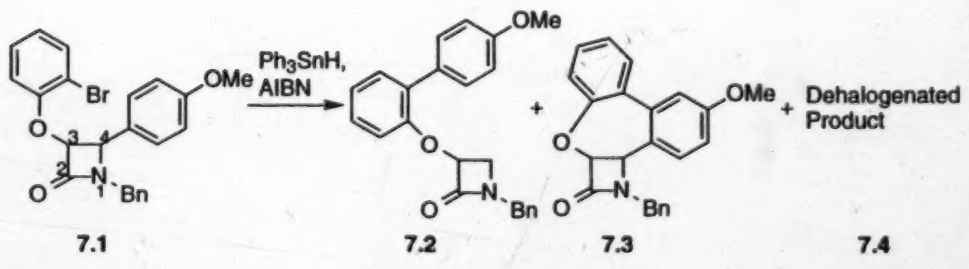
radicals[13] (see **6.5**) and rearomatization are the driving forces for this process.

Treatment of the aryl bromides **6.1** (X = H, CN, CF_3, OMe) with Bu_3SnH/AIBN, using syringe pump addition techniques, and isolation by flash chromatography, gave the biphenyl derivatives **6.6** in moderate yields (34-47%). Tetracyclic compounds **6.7**, arising from a cyclization of the radical at the *ortho*-position, were isolated in 6-13% yield, and the reduced products **6.3** were obtained in 26-28% yield. Hydrolysis of the aryl transfer products **6.6** can subsequently give the required *ortho*-aryl-benzaldehyde derivatives.

Alcaide reported a preliminary study[5g] of an aryl-aryl radical cyclization route to novel polycyclic β-lactam systems.

Substrate **7.1** with the radical precursor on the C(3) group and the aryl acceptor on C(4) of the 2-azetidinone nucleus reacted with Bu_3SnH/AIBN in boiling PhH, to yield the new C(4)-dearylated 2-azetidinone **7.2** (40%) as the main product, together with the cyclization product **7.3** (20%) and

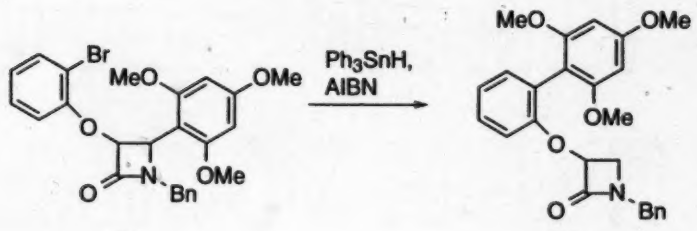
Scheme 7



7.1 **7.2** **7.3** **7.4**

dehalogenated starting 2-azetidinone **7.4** in 15% yield (Scheme 7). Furthermore, analogous treatment of 2-azetidinone **8.1** formed exclusively the rearranged product **8.2** in 80% isolated yield (Scheme 8), showing that the rearrangement process may be facilitated by placing two additional methoxy groups in *ortho* positions on the radical acceptor moiety.

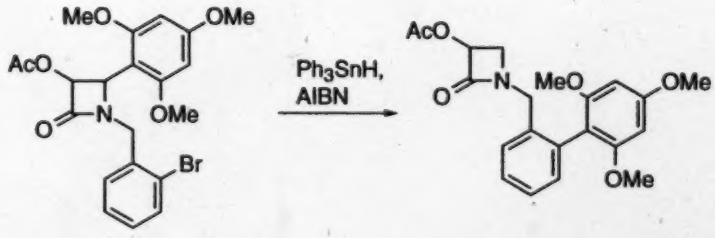
Scheme 8



8.1 **8.2**

To test this hypothesis, 2-azetidinone **9.1** was submitted to Bu_3SnH/AIBN treatment. In fact, C(4)-unsubstituted 2-azetidinone **9.2** was formed exclusively (75% isolated yield) (Scheme 9). On the other hand, the placement of two methoxy groups in *meta* positions, e.g. as in **10.1**, yielded the

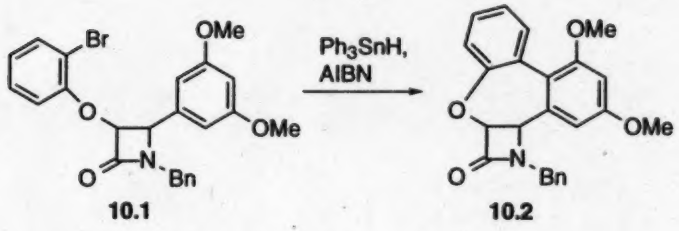
Scheme 9



9.1 **9.2**

cyclization product **10.2** in 60% isolated yield as the sole observed product (Scheme 10).

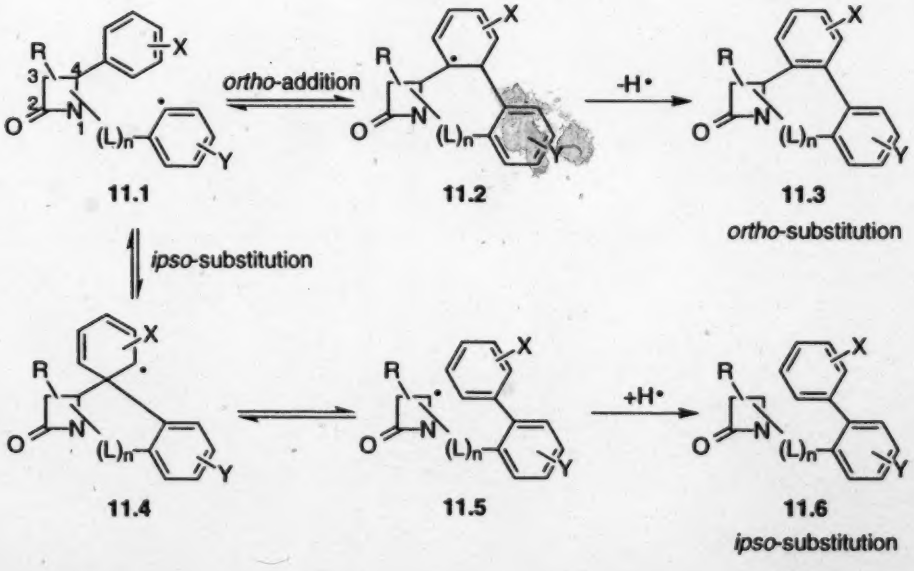
Scheme 10



10.1 **10.2**

The above results show that either cyclization or C(4)-dearylated rearranged products may be obtained regio-selectively by choosing the appropriate structure for the precursor. Thus, placing three methoxy groups at the 2-, 4-

Scheme 11



11.1 **11.2** **11.3**
ortho-substitution

11.4 **11.5** **11.6**
ipso-substitution

and 6- positions (compounds **8.1** and **9.1**) led exclusively to *ipso*-substitution reactions, whereas the presence of two methoxy groups at the 3- and 5- positions (compound **10.1**) resulted in formation of the *ortho*-substitution product (compound **10.2**).

The behavior of the tested substrates may be rationalized as a competition between *ortho*-addition over *ipso*-addition of the initial aryl radical **11.1** (Scheme 11). The competition between the 1,6-addition (*ipso*), and the 1,7-addition (*ortho*) could explain the observed results. Thus, addition of radical **11.1** to the neighboring aromatic ring can operate through an *ipso*-addition to give the spiro-cyclohexadienyl radical **11.4** or alternatively *via* an *ortho*-addition to form the isomeric cyclohexadienyl radical **11.2**. Radical **11.4** benefits from the additional stabilization offered by the oxygen atoms of methoxy groups placed at appropriate positions (*ortho* or *para*) in the radical acceptor ring, and its easy formation then allows breakage of the C(4)-C_{ipso} bond. Regeneration of aromaticity and formation of a more stable azetidin-2-on-4-yl radical **11.5**[13] could provide the necessary driving force for these reactions. In this way, rearranged compounds are obtained as the major or exclusive products of the reactions. Alternatively, the cyclohexadienyl radical **11.2** derived from *ortho* attack would evolve to cyclization product **11.3**, but not to rearranged products. The presence of *meta*-methoxy groups in the radical acceptor ring could lead to direct stabilization of the

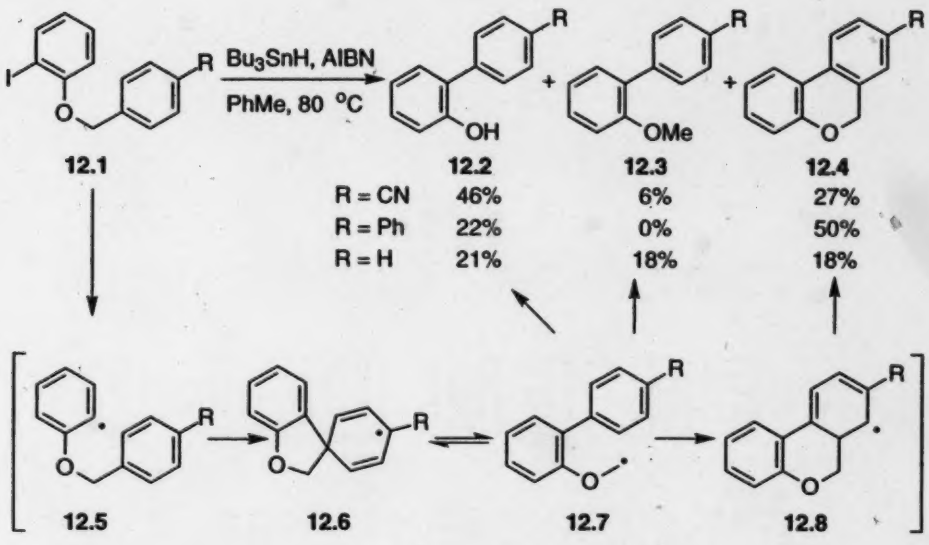
intermediate radical **11.2**, and cyclization product (see **10.2**) is the only observed product in this case. This result clearly indicates that the presence of two *meta* methoxy groups exerts a strong directing effect which totally eliminates *ipso*-substitution products.

Another study on intramolecular addition of aryl radicals to benzyl ethers was carried out by Harrowven,[5k] and the effect of the substitution patterns was also examined in this study.

The *para*-substituted compounds **12.1**, on treatment with Bu_3SnH under standard radical-forming conditions, gave phenol **12.2**, benzo[c]chromene **12.4** and/or methyl ether **12.3**. These results indicate that the reaction proceeds via a 5-*exo-trig* cyclization of **12.5** (Scheme 12). The spirocyclic intermediate **12.6** then fragments to **12.7** to re-establish the aromatic ring. At this juncture many processes compete. Hydrogen atom abstraction from Bu_3SnH gives methyl ether **12.3**. The radical intermediate **12.7** may also add to the arene: a 5-*exo-trig* cyclization leading back to spirocycle **12.6** while the slower 6-*endo*/*exo-trig* course leads to **12.8** and ultimately gives benzo[c]chromene **12.4**. The fragmentation process leading to phenol **12.2** is not understood.

For electron deficient arene **12.1** (R = CN) the phenol generally predominates since the electron-withdrawing substituent disfavors the intermediate **12.8**. In the case of the biaryl benzyl ether **12.1** (R = Ph) the major product

Scheme 12

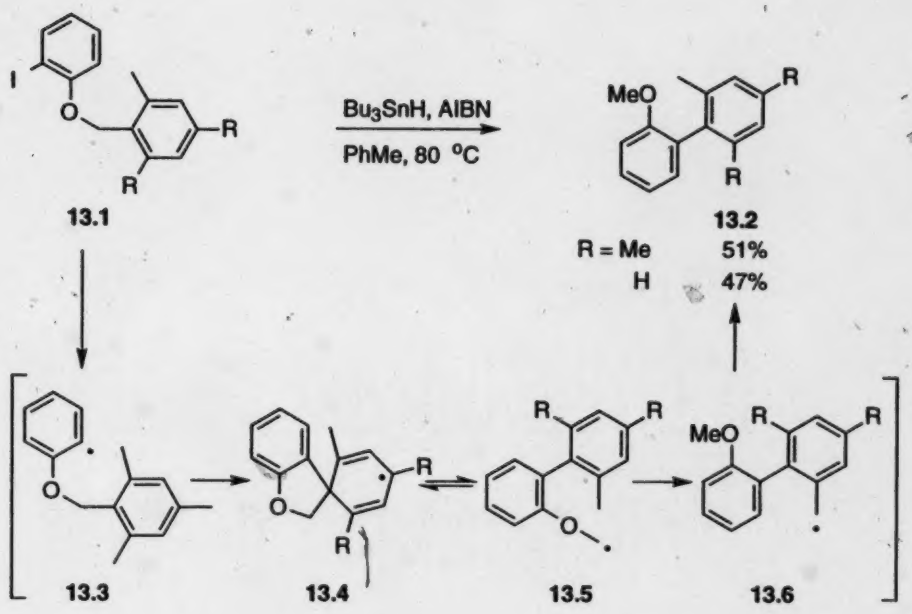


formed (50% yield) was benzo[c]chromene **12.4** (R = Ph).

Blocking the 6-*endo*-*trig* cyclization pathway with one or two *ortho*-methyl substituents also changed the course of the reaction. Exposure of the 2,4,6-trimethylbenzyl ether **13.1** (R = Me) and the *ortho*-methylbenzyl ether **13.1** (R = H) to Bu_3SnH under standard radical-forming conditions gave only methyl ethers (Scheme 13). Since benzyl ether **12.1** (R = H, Scheme 12) gave a complex mixture of products including the phenol, methyl ether and benzo[c]chromene, an intramolecular hydrogen atom abstraction from a proximal methyl group is presumed to operate in the case of **13.1** (see **13.5→13.6**).

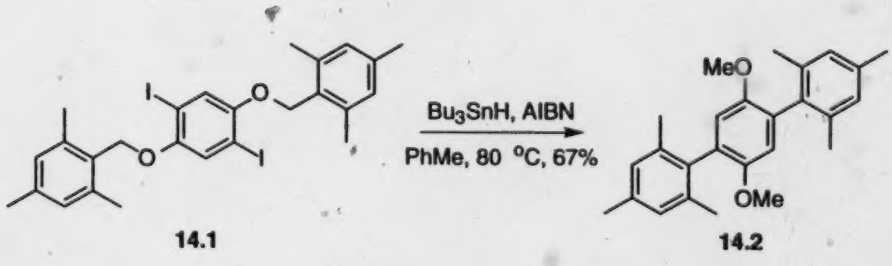
Most interestingly, a remarkable tandem variant of this cascade sequence has also been uncovered. When the reaction

Scheme 13



was tried with diiodide **14.1** the terphenyl **14.2** was formed in 67% yield (Scheme 14).

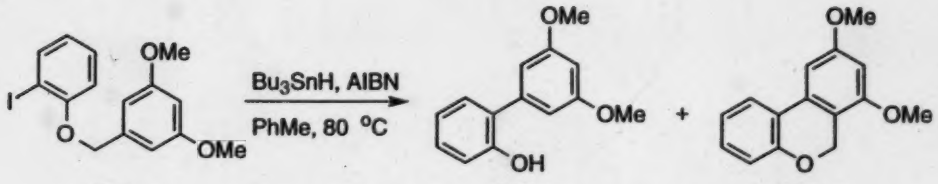
Scheme 14



Likewise, the reaction has been applied to the synthesis of isoaucuparin **15.2**, a natural product found in the sapwood tissue of *Sorbus aucuparia* (Scheme 15).[14] Simply exposing

dimethoxybenzyl ether **15.1** to Bu_3SnH under standard radical-forming conditions gave benzo[c]chromene **15.3** as the major product, together with isoaucuparin **15.2**. The reaction follows the 5-*exo-trig* cyclization-fragmentation-6-*endo*/*exo-trig* pathway of Scheme 12 due to the stabilizing effect of the methoxy groups and the accessibility of the *ortho*-position.

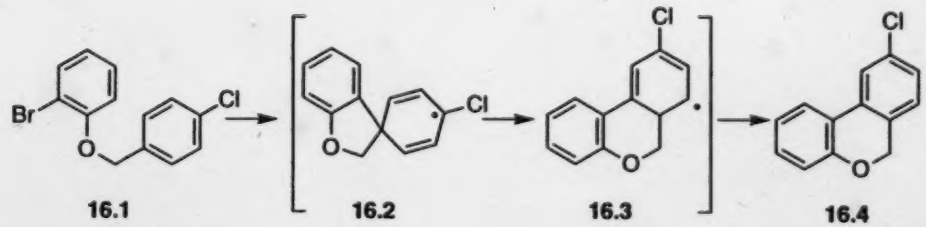
Scheme 15



15.1 → **15.2** 22% + **15.3** 40%

The conversion of benzyl bromoaryl ether **16.1** to benzo[c]chromene **16.4** (Scheme 16) was considered to involve 5-*exo* cyclization from **16.1** to **16.2**, followed by a neophyl rearrangement (**16.2**→**16.3**).[15] However, as aryl iodides **12.1** (R = CN, Ph) provided benzo[c]chromenes **12.4** rather than

Scheme 16



16.1 **16.2** **16.3** **16.4**

17.1, as judged by NOE studies, the migration mechanism outlined in Scheme 16 (R = Cl) does not apply to the reactions of **12.1** when R = CN or Ph.

Scheme 17

12.4 R = CN, Ph **17.1** R = CN, Ph

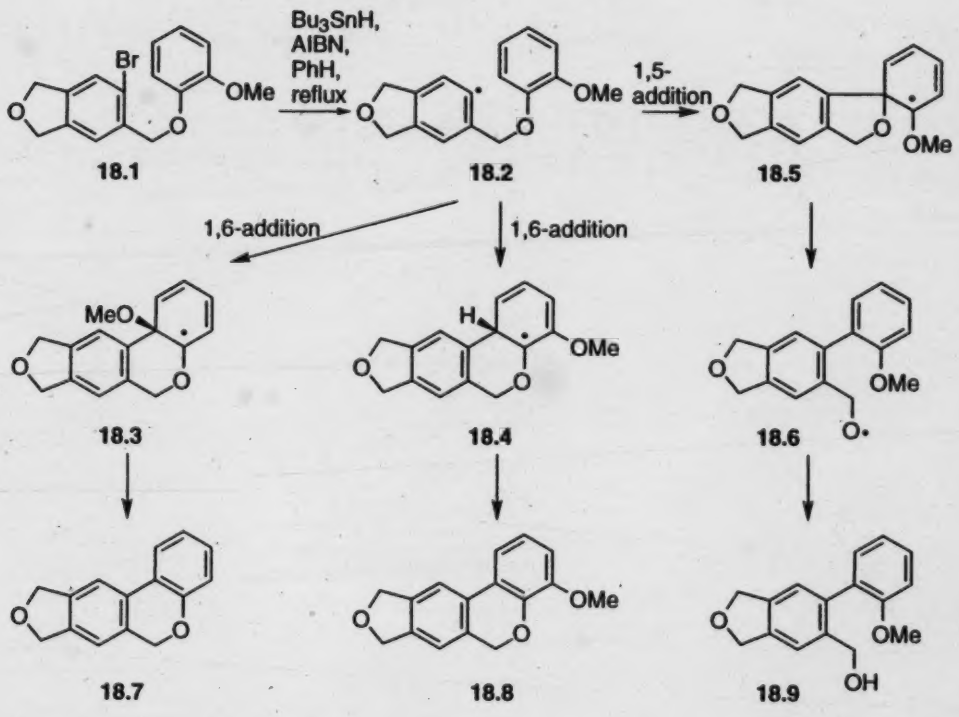
Aryl transfer from oxygen to carbon

Radical transfer from oxygen to carbon to form biaryls has not been studied extensively; only a couple of reports[8e,f] have appeared in the literature, and low yields were obtained in these studies.

The *o*-bromobenzyl phenyl ether **18.1**, with a methoxy group[8e] in the 2-position (*ortho*) of the phenoxy ring, generates the radical intermediate **18.2** on homolysis of the C-Br bond (Scheme 18). The three cyclohexadienyl radicals **18.3**, **18.4** and **18.5** produced on cyclization by 1,6- and 1,5-modes of addition, respectively, all benefit from the additional stabilization offered by the adjacent oxygen atom. While a formal loss of a H atom from **18.4** leads to methoxypyran **18.8** (5.2%), aromatization of **18.3** by ejection of MeO· (β-scission) produces the demethoxylated compound

18.7 (6.8%). A similar β-scission from the spiro-cyclohexadienyl radical **18.5** generates the benzyloxy radical **18.6**, which is quenched in a subsequent fast reaction[16] with Bu_3SnH to form biphenyl alcohol **18.9** (18%). The regeneration of aromaticity is assumed to provide the necessary driving force[17] for these reactions.

Scheme 18

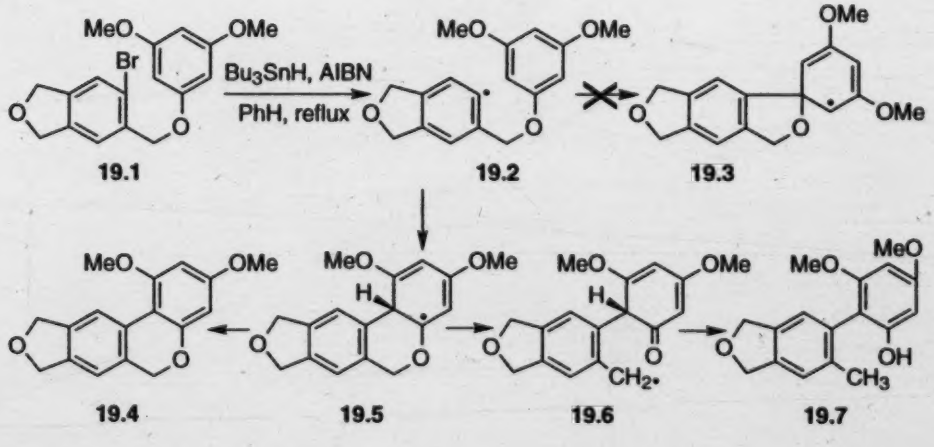


However, when the methoxy group is in a different position on the phenoxy ring a different result is observed. The *o*-bromobenzyl phenyl ether, with a methoxy group in the 3-position (*meta*) of the phenoxy ring, gives the

corresponding methoxypyran (not shown) (20%) as the sole isolable product, where the intermediate radical corresponding to **18.4** finds stabilization from both oxygens. On the other hand, placing the methoxy group in the 4-position (*para*) of the phenoxy ring results in formation of the corresponding methoxypyran (22%) and biphenyl alcohol (7%). Thus, it is clear that the position of the methoxy group governs the nature of the reactions that occur, namely cyclizations with or without loss of substituent and/or the cleavage of the C-O bond.

Placement of two MeO groups at the 3- and 5-positions (double *meta*), so as to permit all the oxygen atoms involved to act in concert to stabilize radical **19.5**, formed by 1,6 attack, led to an interesting result (Scheme 19). The benzylic alcohol resulting from the rearomatization of **19.3** was not found, and so we can conclude that the 1,5 attack of

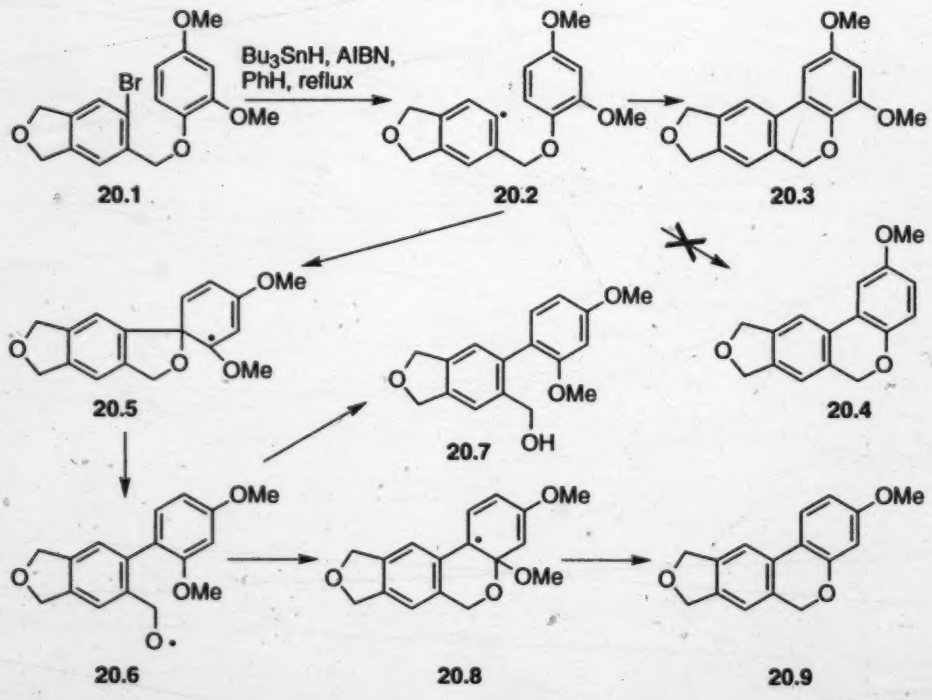
Scheme 19



radical **19.2** is prevented in this case. Instead, the corresponding pyran **19.4** (5%) and phenol **19.7** (27%) were obtained. As indicated above, pyran **19.4** results from formal 1,6-attack and subsequent loss of H·. Formation of the phenol reveals another mode of decomposition available to radical **19.5**. There seems to be a large preference[18] for fragmentation to the ketobenzyl radical **19.6**, and thence to **19.7** by prototropy and reduction or vice-versa.

Attention was next turned to determine the effect, if any, of two MeO groups located in such a way as to encourage 1,5 attack. Accordingly, substrate **20.1** (Scheme 20) was selected and, when subjected to the combined action of Bu_3SnH

Scheme 20



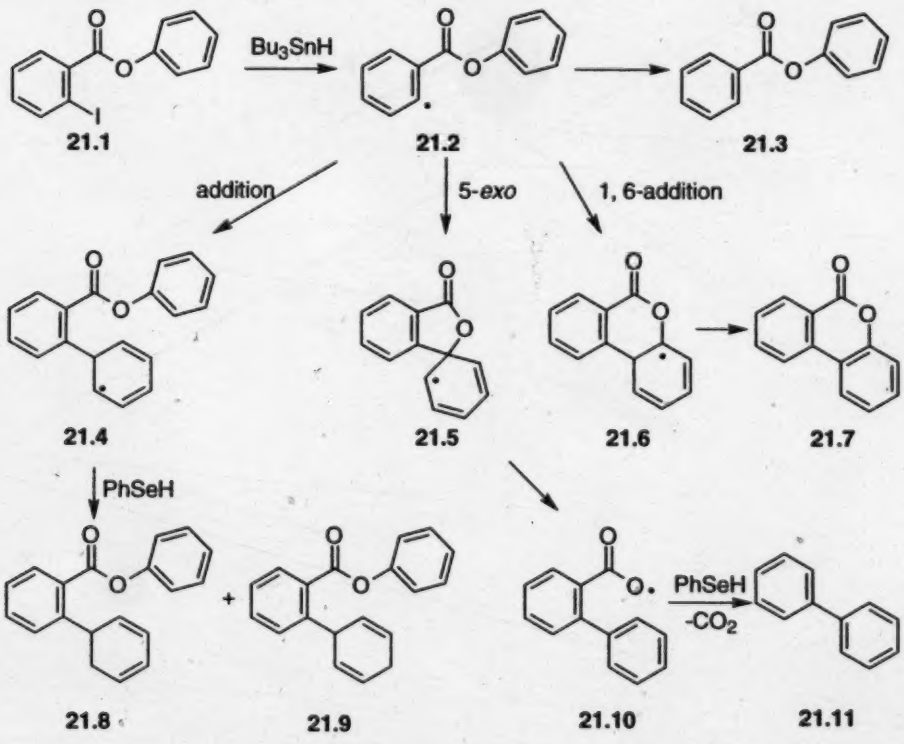
and AIBN, it gave the monomethoxypyran **20.9** (30%), the benzyl alcohol **20.7** (19%) and the dimethoxypyran **20.3** (7.4%). Another product of 1,6 attack from **20.2** should be the 2-methoxy[b,d]dibenzopyran **20.4**. However, this compound was not found. As anticipated, the combined yields (ca 49%) of the products derived from the 1,5 process (**20.7** + **20.9**) significantly outweighed that resulting from the 1,6 substitution (**20.3**, 7.4%).

If a 1,2-oxygen migration takes place in the spiro radical **20.5** to form directly the isomeric radical **20.8**, then the loss of MeO· would furnish 3-methoxy-8,9-methylenedioxy[b,d]dibenzopyran (**20.9**). It is more likely, however, that radical **20.8** is produced from the reactive alkoxyl radical **20.6** by attack on the aryl ring at the carbon bearing the methoxy group.[19]

In Crich's study[8f] on the generation of cyclohexadienyl radicals in the presence of a catalytic amount of PhSeH, substrate **21.1** was examined (Scheme 21). Treatment of **21.1** with a stannane and AIBN in the presence of 20 mol% of PhSeSePh under standard radical conditions gave a mixture of five products with complete conversion of the starting material. Radical **21.2** abstracts H· to form the dehalogenated product **21.3** in 17% yield. Cyclization of **21.2** via a 6-membered ring, followed by loss of H·, gives benzo[c]chromanone **21.7** (12%). The formation of biphenyl **21.11** (21%) arises from a 5-*exo*-*trig* cyclization to give **21.5**, with subsequent expulsion of the carboxyl radical

21.10, and eventual decarboxylation. This process is related to the biaryl synthesis developed by Motherwell.[11f-k,m] The β-elimination of carboxyl radicals is a very rare process but has precedent in the work of Barton, when sufficient thermodynamic driving force, such as gain of aromatic stabilization energy[20] or relief of ring strain,[21] is available. Moreover, two new, inseparable products were

Scheme 21



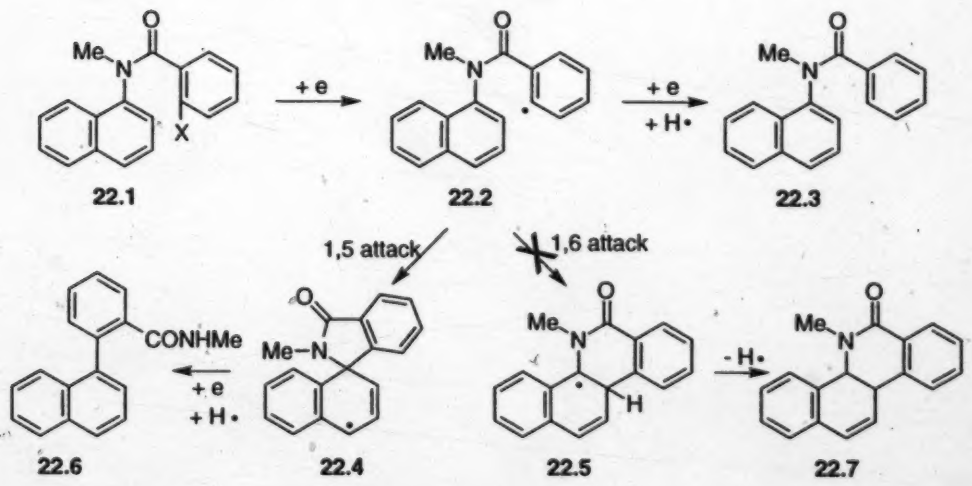
formed with a combined yield of 40%. These products were assigned structures **21.8** and **21.9** and are derived from addition of the initial aryl radical to the solvent PhH,

followed by trapping with the selenol. Inspection of the NMR spectra of the crude reaction mixtures showed that in the absence of PhSeSePh products **21.8** and **21.9** were formed in only trace amounts.

Transfer from nitrogen to carbon

A study[9a,b] on the electrochemical reduction of aryl halides showed that the phenyl radical **22.2**, initially formed by reductive cleavage of the carbon-halogen bond, can be trapped in good yield by reaction with the adjacent benzene ring (Scheme 22). Electrochemical reduction of 2-halogeno-*N*-methyl-*N*-(1-naphthyl)benzamides afforded the amide **22.3** and the biaryl derivative **22.6**. Product **22.3** arises by reduction of **22.2**. Radical **22.4**, the 1,5-attack product from **22.2**, was reduced further at the electrode with cleavage

Scheme 22



of a carbon-nitrogen bond, and the biaryl **22.6** was isolated in 69% yield. However, no *N*-methylbenzo[c]phenanthridone **22.7**, the 1,6 attack product, could be detected in these reactions. To explain this behavior, steric effects are proposed to cause a rotation of the *N*-aryl ring out of the plane of the amide function so that the reacting carbon atoms required for the conversion of **22.2** to **22.4** are closer than the reacting carbon atoms required for conversion of **22.2** to **22.5**, i.e. entropy of activation favors the formation of **22.4** from **22.2**.

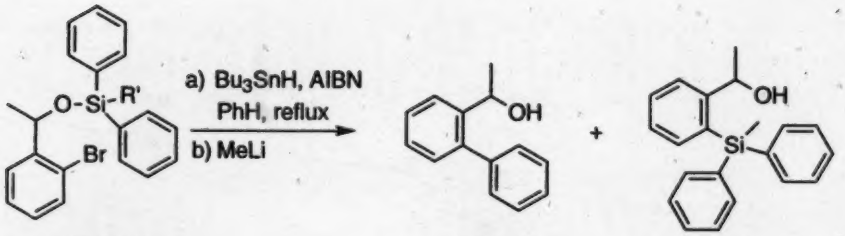
Electrochemical reduction of 2-bromo-*N*-methyl-*N*-(1-naphthyl)benzamides is an attractive route for the synthesis of some derivatives of 1-phenylnaphthalene. However, during reduction of the corresponding 2-iodo compound, replacement of the halogen by hydrogen becomes the predominant reaction and the isolated yield of **22.6** falls to about 20%.

Aryl transfer from silicon to carbon

Phenyl migration from silicon to *C*-centered radicals has been used in the preparation of biaryls.[10f] The attacking aryl radical was linked with the migrating aryl group by a silyl ether functionality. In this way, the silicon tether has been used to transform an intermolecular reaction to an intramolecular process, a concept often called the "Stork temporary silicon connection".[22] However, in the aryl migration reactions from Si to aryl radicals discussed here, the tether is cleaved during the reaction. The phenyl

migrations (Scheme 23) occur under the standard radical conditions (stannane/AIBN in refluxing PhH). Desilylation, using MeLi, afforded, after chromatography, the desired biphenyl derivatives **23.2** along with silylated benzyl alcohol **23.3**. The side product **23.3** derives from

Scheme 23



	23.1A-F	23.2	23.3
A	R' = $SiMe_3$	55%	28%
B	R' = $GeMe_3$	52%	39%
C	R' = $SnMe_3$		84%
D	R' = CMe_3	56%	
E	R' = Me	52%	
F	R' = Ph	71%	

intramolecular homolytic substitution at silicon (S_Hi)[23] and subsequent opening of the intermediate cyclic silyl ether with MeLi (Scheme 24).

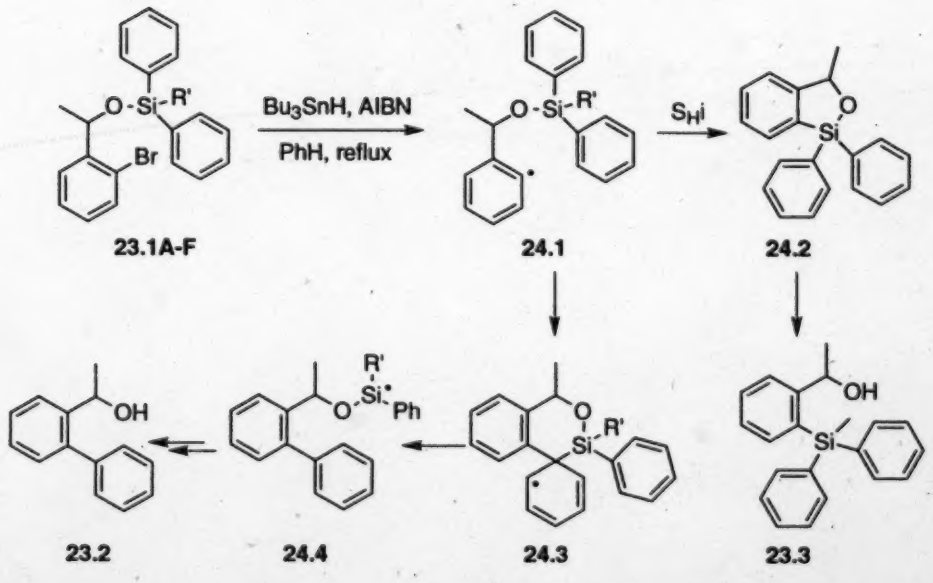
No biphenyl product was found in the reaction of stannylated silyl ether **23.1C**, and the S_Hi-derived alcohol **23.3** was isolated in 84%. Phenyl migration to the aryl radical generated from **23.1C** is too slow to compete with the S_Hi reaction. For germylated or silylated silyl ethers, the S_Hi reaction with primary alkyl radicals is about 100-1000 times slower than the corresponding reaction with stannylated

silyl ethers.[23a] Indeed, the phenyl migration product **23.2** is the main product in the reaction of **23.1A** (55%) and the S_Hi-derived alcohol **23.3** was isolated in only 28% yield. Similar results were obtained for the germylated silyl ether **23.1B**, where biphenyl **23.2** was isolated in 52% yield along with 39% of the side product **23.3**.

To completely suppress the S_Hi reaction, the heavier group 14 substituent (R' in Scheme 23) was replaced by an alkyl or a phenyl group. For all these diphenylsilyl ethers (**23.1D–23.1F**), biphenyl **23.2** was isolated in good yields (52-71%).

For the phenyl migration, the following mechanism (Scheme 24) was suggested. Depending on the substituent R', aryl radical **24.1** undergoes either an S_Hi reaction at silicon

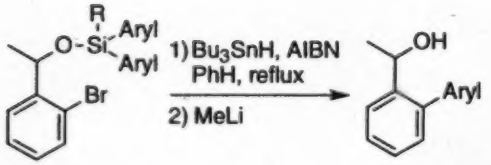
Scheme 24



to form the cyclic silyl ether **24.2** or *ipso* attack to form radical **24.3**, which then rearomatizes to silyl radical **24.4**. Radical **24.4** can react with solvent PhH in a homolytic aromatic substitution.[24] Desilylation (MeLi) then affords the biphenyl **23.2**. In the other reaction pathway, ring opening of **24.2** with MeLi eventually leads to alcohol **23.3**.

It is also possible to transfer functionalized aryl groups from silicon to aryl radicals (Scheme 25). With the *p*-fluoro derivative **25.1A**, the aryl migration product **25.2A** was formed in 49%. With the *tert*-butylated silyl ether **25.1B**, the transfer product was obtained in 35%. The best result was seen in the transfer of the *p*-methoxyphenyl group (**25.1C→25.2C**, 77%).

Scheme 25



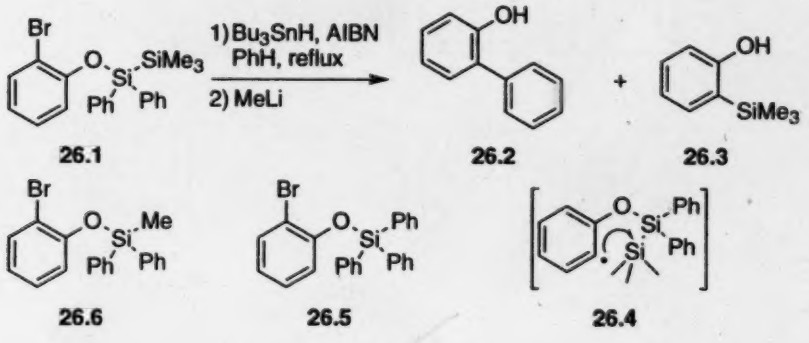
25.1 25.2

	Aryl	R	Yield
A	*p*-F-C_6H_4	$SiMe_2Ph$	49%
B	*p*-F-C_6H_4	*t*-Bu	35%
C	*p*-MeO-C_6H_4	Me	77%

The above transformations are 1,5 phenyl migrations. A 1,4 phenyl migration from silicon to an aryl radical was also investigated (Scheme 26). Transformation of **26.1** afforded silylated phenol **26.3** as the major product in 50% yield, along with the desired biphenyl derivative **26.2** (38%), resulting from 1,4-phenyl migration. Phenol **26.3** is formed

via initial S_Hi reaction at silicon (see **26.4**). Obviously, the transition state for 4-*exo* attack at the silicon attached to the oxygen atom is too strained and 5-*endo* attack at the distal silicon atom occurs, in addition to *ipso* attack (minor pathway). Interestingly, no products derived from *ortho* (i.e. 6-*exo*/*endo*) attack on a phenyl group were observed.

Scheme 26



26.1 **26.2** **26.3** **26.6** **26.5** **26.4**

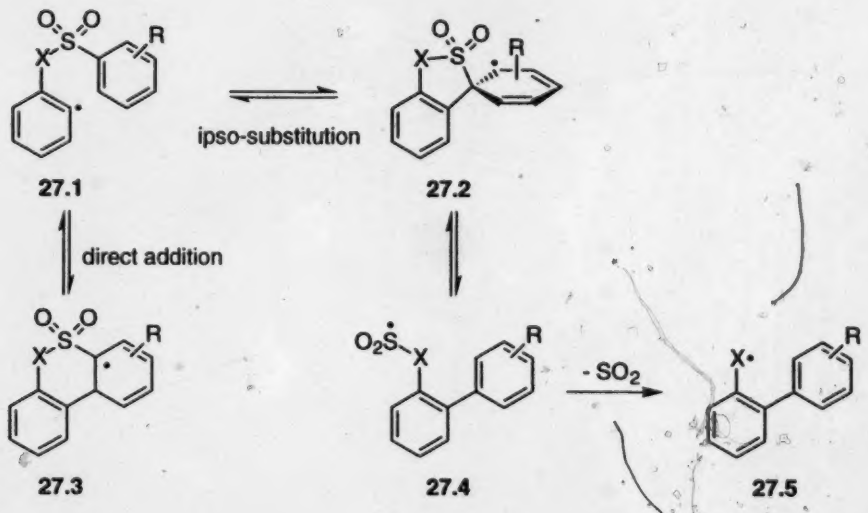
To suppress the S_Hi reaction, the trimethylsilyl group in **26.1** was replaced by a phenyl group (see **26.5**). However, neither phenyl migration nor dehalogenation was observed. Also, in the case of the compound **26.6**, bearing a Me instead of a Me_3Si group, no radical reaction was observed, and for both **26.5** and **26.6** only starting material was obtained. Although the X-ray structure of **26.5** shows that the bromine is not protected by the silyl group in the solid state and reaction with tin radicals seems to be feasible, it is possible that the bulky silyl group protects the bromine from attack when the trimethylsilyl group in **26.1** is replaced by a

phenyl group.

Transfer from sulfur to carbon

Motherwell has developed an intramolecular free radical *ipso*-substitution approach[11f,i,j,m] based on the SO_2 group as a tether between two aromatic rings that are subsequently linked (Scheme 27). The reaction pathway proceeds *via* the spirocyclic intermediate **27.2** which is capable of rearomatization through loss of SO_2 thereby avoiding the alternative direct addition process (**27.1→27.3**). Both the nature and the number of atoms (X) in the tethering

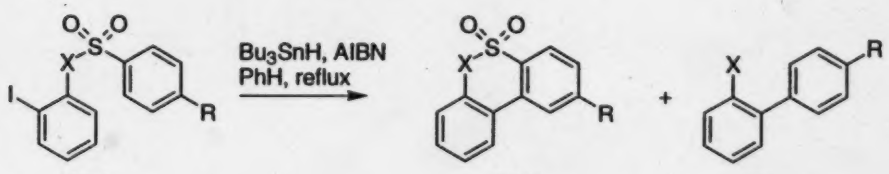
Scheme 27



chain and the location and electronic character of substituents (R) on the sulfonyl-substituted acceptor ring are expected to play pivotal roles in this mechanism.

In the first example shown in Scheme 28, a competition between [1,5] *ipso* substitution and direct [1,6] addition is involved. The latter is preferred in the sulfonate derivatives (X = O), while [1,5] *ipso*-substitution is favored in the sulfonamide derivatives (X = NMe). Since the decarboxylation of carbamoyloxyl radical ($R_2NCO_2\cdot$) is known to be faster than the analogous oxygen case ($ROCO_2\cdot$),[25] it may be that there is a similar rate difference for extrusion of SO_2, and if this is indeed the case, the above results are easy to understand.

Scheme 28



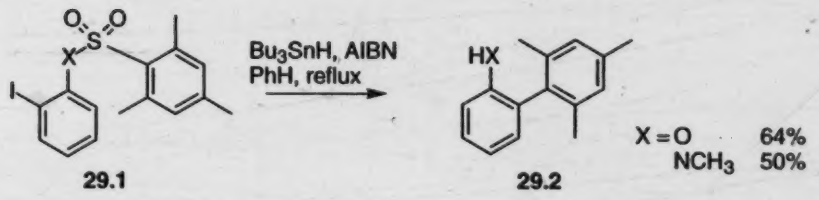
28.1		28.2	28.3
X = O	R = CH_3	63%	0
NCH_3	CH_3	39%	34%
O	OCH_3	24%	18%
NCH_3	OCH_3	10%	33%

If the *para*-methyl group is replaced by a *para*-methoxy group, the ratio of **28.3** [1,5] over **28.2** [1,6] rises. Incorporation of substituents on the aromatic acceptor ring facilitates [1,5] *ipso*-substitution by stabilizing an adjacent carbon radical. In addition, on changing the *para*-methyl group of **28.1** to an *ortho*-methyl group, in which one of the possible sites for [1,6] addition is blocked, the amount of [1,5] product **28.3** rises from 0% to 23%, and the amount of [1,6] addition product **28.2** drops from 63% to 36%

(X = O).

As anticipated, the reaction of the corresponding mesityl derivatives **29.1** led to a cumulative enhancement of the preference for the [1,5] process, and no dihydroaromatic or rearranged products derived from the competing [1,6] addition were isolated (Scheme 29).

Scheme 29

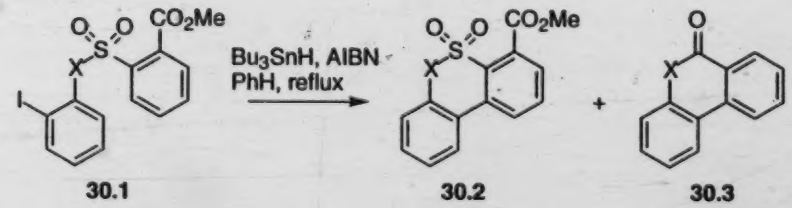


29.1 **29.2**

The results shown in Schemes 30 and 31 clearly indicate once again that the location of the substituents on the aromatic acceptor ring plays a very important role in determining the reaction pathway.

The carbomethoxy group adjacent to the sulfonyl moiety is a highly efficient *ipso* director, while for the correspon-

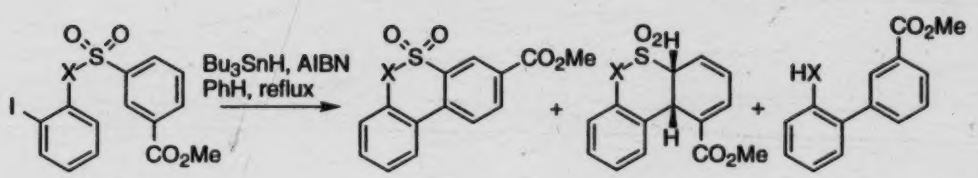
Scheme 30



30.1 **30.2** **30.3**

X=O 21% 42%
NCH3 19% 65%

Scheme 31



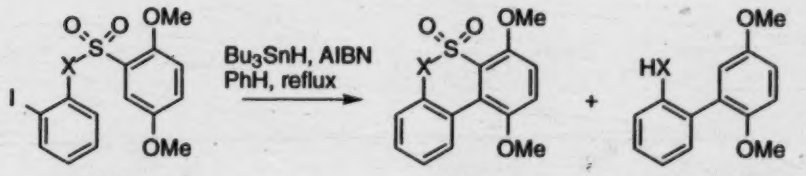
31.1	31.2	31.3	31.4
X = O	52%	19%	0%
NCH_3	37%	11%	28%

ding substrates **31.1** in the *meta* series, the inherent tendency for the sulfonamide linkage to favor *ipso* substitution is opposed by the *meta* location of the carbomethoxy group, and a product distribution favoring [1,6] addition was obtained. The corresponding sulfonate provided two distinct types of products both derived solely from [1,6] addition at the two possible sites of attack. It was of interest to note that, while the usual oxidation to aromatics under tin hydride reduction conditions occurred for one set of regioisomers (**31.2**), only the dihydroaromatic derivatives **31.3** were isolated from the second set. Presumably this is a consequence of the fact that aromatization would have led to the introduction of a severe *peri* interaction from the carbomethoxy group.

As seen above (Scheme 28) a *para* methoxy group is more efficient in promoting *ipso* substitution than a *para* methyl group. For the dimethoxy derivative **32.1** (Scheme 32), the results clearly indicate once again that the location of the methoxy group adjacent to the sulfonyl group is exerting a

dominant directing effect which either minimizes or totally eliminates [1,6] addition products **32.2**, even in the presence of a *meta* methoxy group.

Scheme 32



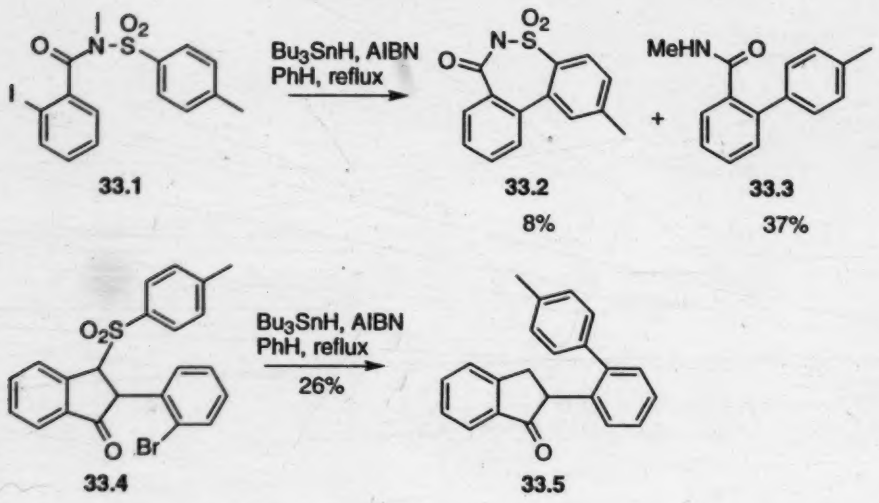
32.1 X = O, NCH_3 | **32.2** 7%, 0% | **32.3** 43%, 63%

Interestingly, the products derived from direct addition are significantly diminished by lengthening the linking chain X (Scheme 33), providing more opportunities for [1,6] *ipso*-substitution (see **33.3** and **33.5**).

This tendency for addition could be effectively counteracted once again by the introduction of dominant *ortho*-substituents, as shown by the representative examples in Scheme 34, thereby reinforcing the earlier observations in the study of [1,5] *ipso* substitution reactions and providing further evidence that this approach is especially suited for the preparation of more hindered biaryls, such as **34.2**.

The powerful directing effect exerted by the *ortho* carbomethoxy substituent in the high-yielding conversion of sulfonate **34.3** is particularly noteworthy. It was also of interest to observe that lactone **34.5** is formed, possibly as

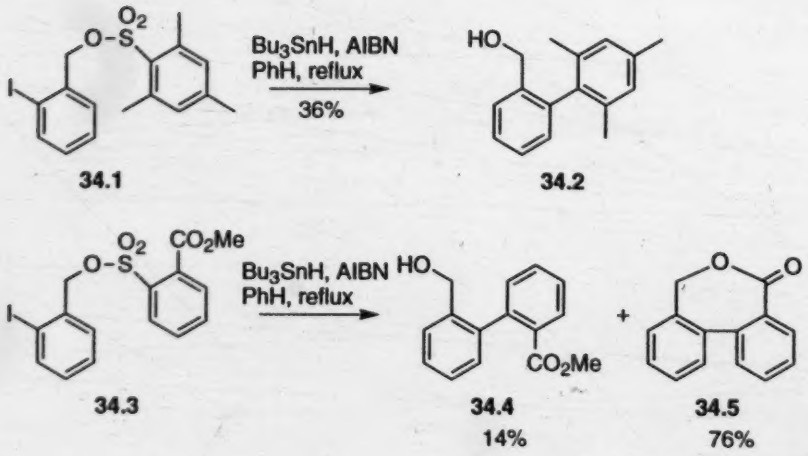
Scheme 33



33.1 → 33.2 (8%) + 33.3 (37%)

33.4 → 33.5 (26%)

Scheme 34



34.1 → 34.2 (36%)

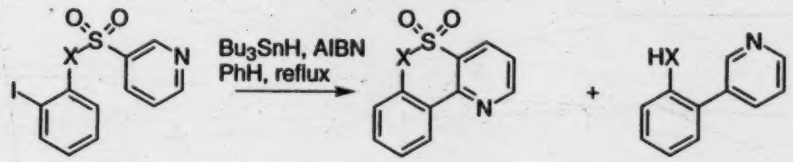
34.3 → 34.4 (14%) + 34.5 (76%)

a result of a tributyltin iodide-mediated transesterification.

As the examples shown in the following three Schemes indicate, the presence of an appropriately placed heteroatom

allows the synthesis of heterobiaryls. These representative examples reinforce the previously established reactivity patterns.

Scheme 35

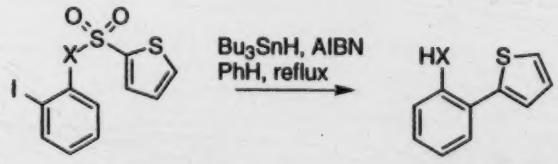


35.1 X = O, NCH_3 | **35.2** 43%, 33% | **35.3** 0%, 29%

Thus, the reactions of **35.1** can be readily understood by analogy with the behavior of compounds having the *meta*-substituted benzene instead of the pyridine unit, leading, as expected, to a preference for [1,6] direct addition, giving **35.2**.

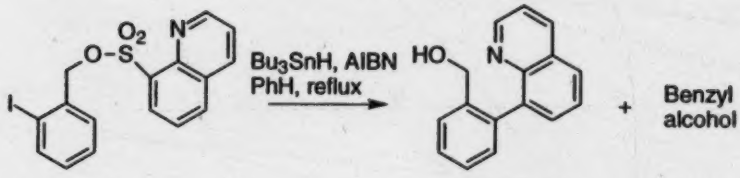
The thiophene **36.1** (Scheme 36), like *ortho*-substituted compound **29.1**, gave only the [1,5] *ipso* substitution products **36.2**.

Scheme 36



36.1 X = O, NCH_3 | **36.2** 50%, 69%

Scheme 37

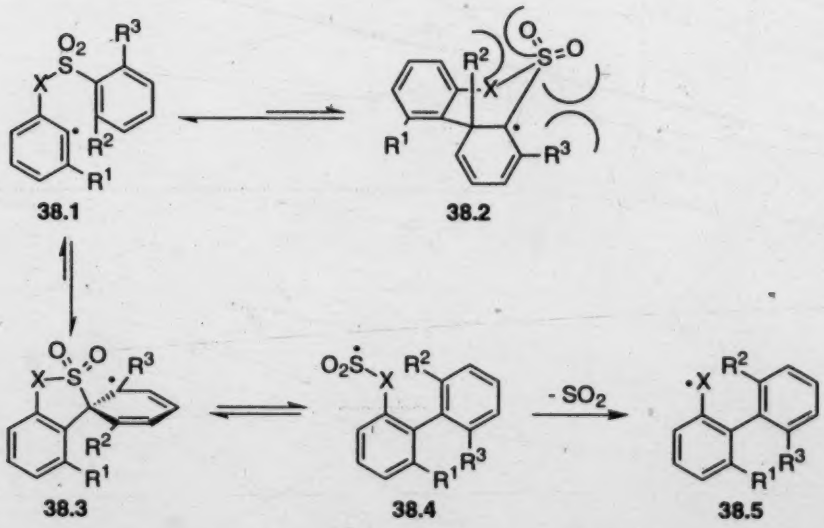


37.1 37.2 46% 21%

For the quinoline derivative **37.1**, the [1,6] *ipso* substitution product **37.2** was formed in 46% yield. However, the isolation of benzyl alcohol from this reaction may be indicative of competitive stannyl radical-induced cleavage of the heterocyclic sulfonate linkage of the starting material.[26]

In the previous studies of the [1,5] *ipso* substitution pathway, the presence of either electron-donating and/or electron-withdrawing substituents R^2 and R^3 *ortho* to the

Scheme 38

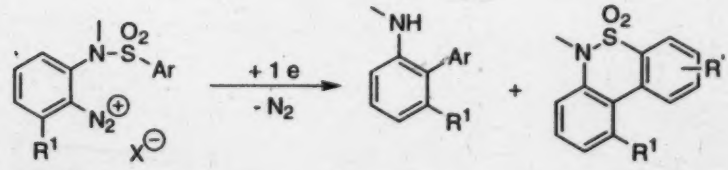


38.1 38.2 38.3 38.4 38.5

sulfonyl group (Scheme 38) had a significant effect in promoting *ipso* substitution. In addition, the involvement of spirocyclic intermediate **38.3** suggests that the incorporation of an additional substituent R^1, adjacent to the σ aryl radical, should not only reinforce the least hindered orthogonal approach of the two aromatic rings but also increase the steric interactions developing in the competing direct addition pathway. As a result, the formation of a hindered biaryl should be favored.

Motherwell also used arenediazonium salts as radical precursors (Scheme 39). The diazonium salts **39.1** were treated with electron donors, such as CuCl and $TiCl_3$, and gave [1,5] *ipso* substitution products **39.2** and [1,6] direct addition products **39.3**. In terms of the relative ratios of *ipso* substitution versus addition, **39.1A** and **39.1B** mirror the pattern previously observed (Scheme 28 and 29) in the reduction of iodoarenes with Bu_3SnH, with the mesityl group on the sulfonyl-substituted aromatic acceptor ring clearly disfavoring direct addition.

Scheme 39



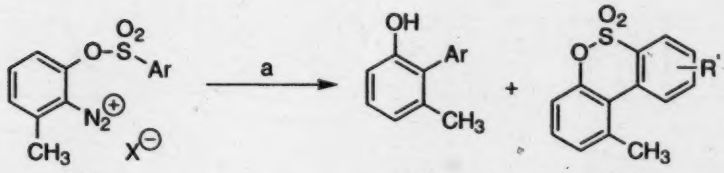
39.1 **39.2** **39.3**

	R^1	Ar		
A	H	4-methylphenyl	55%	25%
B	H	mesityl	60%	0
C	CH_3	mesityl	73%	0

Incorporation of the additional methyl group *ortho* to the σ aryl radical donor (as in **39.1C**) appears to favor *ipso* substitution, as the yield was increased to 73%. This suggests that hindered biaryls can be formed by this type of transformation.

In the corresponding sulfonate series (Scheme 40), the results were quite different from the previous observations (see Scheme 28) using Bu_3SnH. The sulfonate is a much less

Scheme 40



40.1 **40.2** **40.3**

Ar		
4-methoxyphenyl	68%	4%
4-methylphenyl	69%	8%
mesityl	82%	0

a: $TiCl_3$, aq HCl, acetone, 0 °C

effective linking chain than the sulfonamide in terms of isolated yields of *ipso* substitution products. When the diazonium salts **40.1** were subjected to $TiCl_3$ reduction, *ipso* products **40.1** were formed in very good yields, and this tin-free route gives higher isolated yields of *ipso* substitution products.

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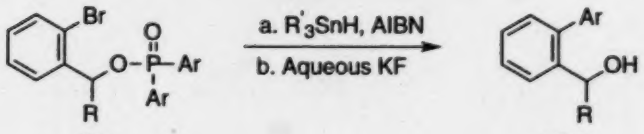
Results and discussion

My first project resulted in the discovery that halo phosphinates undergo aryl transfer, as summarized in Scheme 41, to afford biaryl derivatives by radical *ipso*-substitution.[1] Such transfer from phosphorus to carbon had not been reported before. This reaction was observed during studies aimed at a very different result.

Scheme 41

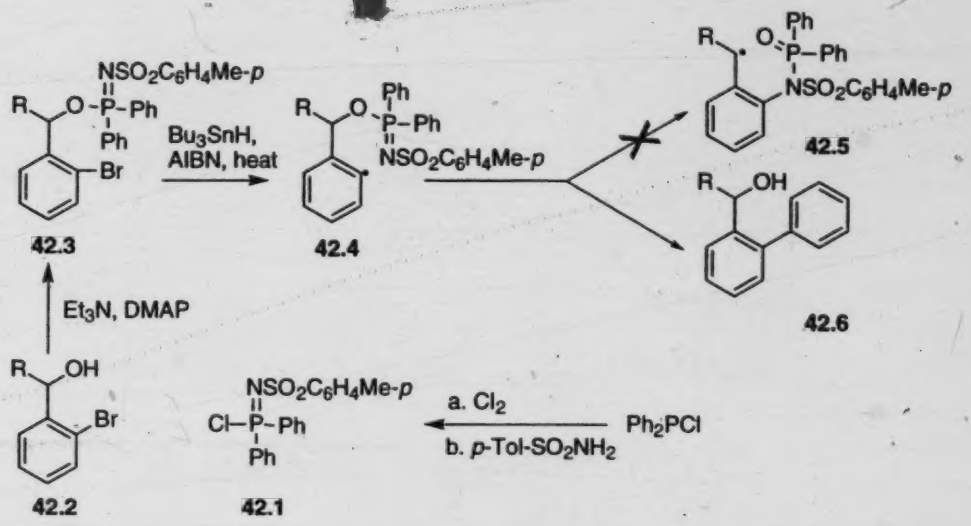


41.1 **41.2**

Considerable attention has been directed toward the synthesis of nitrogen-containing natural products,[2] such as alkaloids, and my first project started as an attempt to develop a new method for making amines by using radicals. To this end, compounds **42.3** were made from 2-bromobenzyl alcohols **42.2** and *p*-toluenesulfonamide derivative **42.1** under basic conditions. The alcohols **42.2** were themselves produced from commercially available 2-bromobenzaldehyde and $NaBH_4$ (R = H), MeMgBr (R = Me), or PhMgBr (R = Ph). Compound **42.1** was made in two steps by the literature procedure[3] from Ph_2PCl.

In compounds of type **42.3**, we believed that the derived radicals **42.4** would rearrange to **42.5** because formation of a strong P=O double bond[4] would be the driving force for

Scheme 42



replacement of the O-P=N bond system by O=P-N. The rearrangement of radicals of type **42.4** to **42.5** would resemble the well-known[5] β-(phosphatoxy)alkyl and β-(acyloxy)alkyl radical rearrangements.

Under standard conditions for radical rearrangement, we were surprised to find that the aryl transfer products **42.6** (R = H, 45%; R = Me, 50%; R = Ph, ca 15%) and *p*-toluenesulfonamide were formed, and none of the desired nitrogen transfer product was isolated. In one of these experiments we obtained a crystalline compound (**42.6**, R = Me), and analysis of its NMR, IR, and mass spectra enabled us to deduce the structure and suggest a reasonable mechanism. We appreciated that radical **42.4**, generated by homolytic fission from the bromo derivatives **42.3**, might be trapped by the solvent (PhH),[6] rather than by intramolecular transfer.

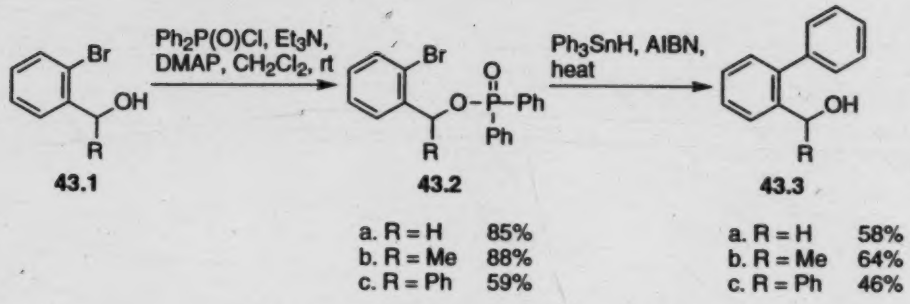
For this reason, we changed the solvent to PhMe, but once again the same phenyl substituted biaryl derivative was obtained. We were pleased by the fact that we had discovered a new method for making biaryls. As described in the review section, Motherwell had made biaryls by using the SO_2 group as a tether (see Introduction of this chapter), but transfer from phosphorus was not known.

Our results with compounds **42.3** suggested that the nitrogen subunit of **42.3** might play little role on the course of the reaction. Therefore, we prepared several phosphinates, i.e. we replaced the nitrogen subunit by oxygen, and it was quickly established that the nitrogen subunit is indeed unnecessary and that the aryl transfer is a characteristic of phosphinates, as summarize in Scheme 41. We then established the generality and scope of the process, optimized the reaction conditions and tried to identify the mechanistic details, as described below.

General preparation of phosphinates and their radical rearrangement reactions

As mentioned above, we replaced the $P{=}NSO_2Tol\text{-}p$ function by a simple P=O double bond. This was done by phosphinylating alcohols **43.1** with commercially available $Ph_2P(O)Cl$ or by using the reagent made in-house by treating Ph_2PCl with ozone.[7] Under standard conditions (Et_3N, catalytic amount of DMAP, CH_2Cl_2 as the solvent, room temperature, ca 1 h), the phosphinylation of alcohols **43.1**

Scheme 43



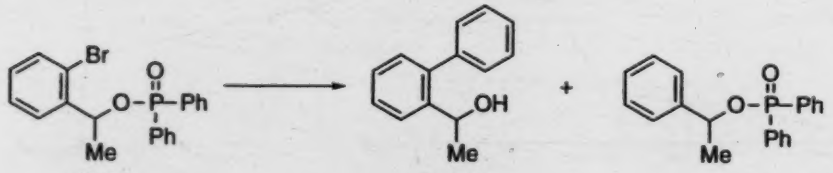
worked in good yields.

The general procedure for the radical rearrangement involves slow addition of a solution of stannane and AIBN to a refluxing hydrocarbon solution of the phosphinate, the stannane and initiator usually being added in a single solution by syringe pump over ca 10 h. Standard high dilution conditions were employed, with the reagent solution being 0.03-0.06 M in stannane and 0.006-0.016 M in initiator. The amounts of stannane and initiator were 2 mol per mol of substrate and 0.5 mol per mol of substrate, respectively. The amount of AIBN was arbitrary, but more than 1.5 (and probably 2) mol of stannane per mol of substrate are required (see details in the section on mechanistic studies).

We optimized the radical reaction conditions using compound **43.2b** (Scheme 44). As indicated, higher solvent boiling points resulted in an increase in the yield of the transfer product, and a decrease in the amount of the simple reduction product. Reactions done in xylene gave better yields than those in low-boiling hydrocarbons (PhMe and PhH),

at least as judged by experiments with **43.2b**, and so we generally used xylene as the solvent. PhMe and PhH, however, were used in some cases (see Table 1, entries 7, 11, 12, 15 and 16, pages 85 and 86).

Scheme 44



43.2b (S.M.) **43.3b** (D.P.) (R.)

Reaction conditions; Workup	D.P.%	R%	S.M.%
Ph_3SnH, AIBN, xylene, reflux; KF-H_2O	57%	-	-
Ph_3SnH, AIBN, toluene, reflux; KF-H_2O	46%	20%	-
Ph_3SnH, AIBN, benzene, reflux; KF-H_2O	43%	25%	-
Ph_3SnH, AIBN, xylene, reflux; K_2CO_3-MeOH	64%	-	-
Ph_3SnH, AIBN, $(PhSe)_2$, xylene, reflux; KF-H_2O	20%	17%	20%
Ph_3SnH, Et_3B, air, hexane, rt; KF-H_2O	19%	-	72%

Usually, the reaction mixture was evaporated and treated with saturated aqueous KF, followed by chromatography, but in some cases, other workup conditions were used (see Table 1, entries 8 and 9). For the experiments summarized in Scheme 43, the crude reaction mixture was stirred with methanolic K_2CO_3, in the mistaken belief that the isolated alcohol was the product of hydrolysis occurring during workup. We did get a better yield with methanolic K_2CO_3 (Scheme 44, 64%) than with KF-water (57%). We soon gained the impression, however, that the isolated alcohols were already present in the xylene solution before workup when we carried out the mechanistic

study, and so we used KF[8] in most subsequent workup procedures (to help in removal of the tin species). In a couple of cases (see Table 1, entries 8 and 9), however, higher yields were obtained when the workup was done with $NaCNBH_3$[9] rather than KF (44% versus 6% for entry 8, and 17% versus 7% for entry 9).

In order to improve the yield of the radical reaction, the presence of catalytic amounts of PhSeH, generated *in situ* by stannane reduction of PhSeSePh, was tried. By analogy to Crich's study on stannane-mediated radical addition to arenes, we felt that this modification might raise the yield.[6] However, a low yield of transfer product was obtained, as well as the reduced product, and starting material was recovered.

Et_3B, in the presence of air, has often been used as an initiator,[10] and so we tried it in our system. Even though no reduced product was isolated, using **43.2b**, the desired transfer product was obtained in low yield, and starting material was the main substance recovered.

Ph_3SnH was generally used; however, in some cases Bu_3SnH gave a higher yield [see Table 1, entries 10 (41% versus 36%) and 15 (27% versus 17%)]. For Table 1, entries 7 and 16, Bu_3SnH was arbitrarily tried. However, we did not carry out a systematic survey of the relative merits of the two stannanes.

In summary, Ph_3SnH and AIBN in refluxing xylene, followed by aqueous KF workup and chromatography, were the

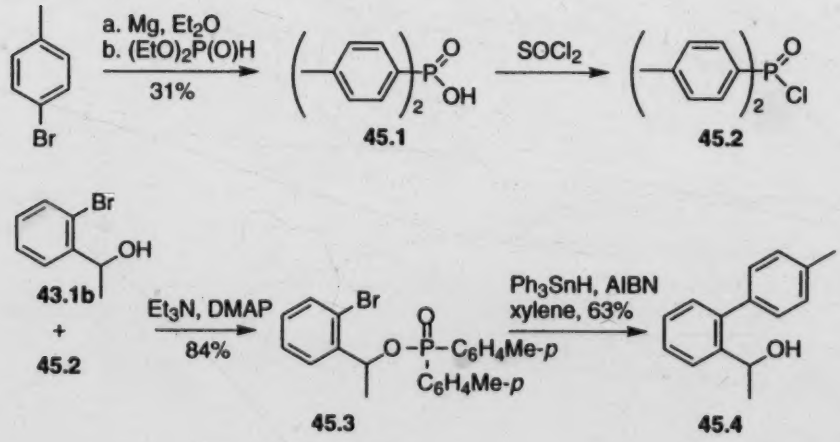
general reaction conditions that we used for the radical rearrangement.

Variation of transferred aryl group

In order to establish the generality of the radical rearrangement, we first examined the effect of changing the functional group on the migrating aryl ring, as well as the nature of that ring – aromatic versus heteroaromatic.

p-Toluenephosphinic acid **45.1** was made by the literature procedure[11] from diethyl phosphate and the Grignard made from *p*-bromotoluene and magnesium. The corresponding phosphinic chloride was made from the phosphinic acid by chlorination using an excess of $SOCl_2$. The crude phosphinic chloride was

Scheme 45

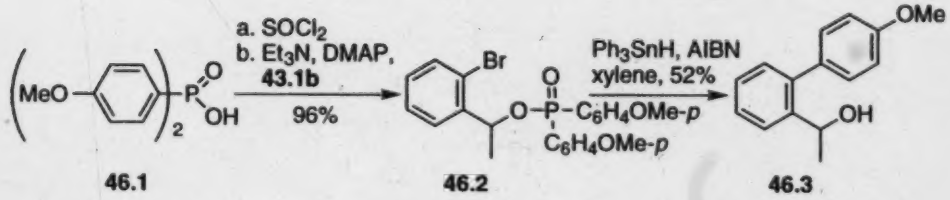


used directly for reaction with the benzyl alcohol **43.1b**, in the presence of Et_3N in CH_2Cl_2, producing phosphinate **45.3** as

a thick, pale yellow oil in 84% yield. Finally, the purified phosphinate **45.3** was subjected to the standard radical reaction conditions in xylene to generate the transfer product **45.4** as a white solid in 63% yield. In this case, the *para*-substituted product was obtained from the *para*-substituted starting material, and so the operation of an *ipso*-attack mechanism is obvious. (The mechanistic study will be discussed in detail in a later section).

We then examined the effect of replacing the *para*-methyl group on the migrating aryl ring by a *para*-methoxy group.

Scheme 46

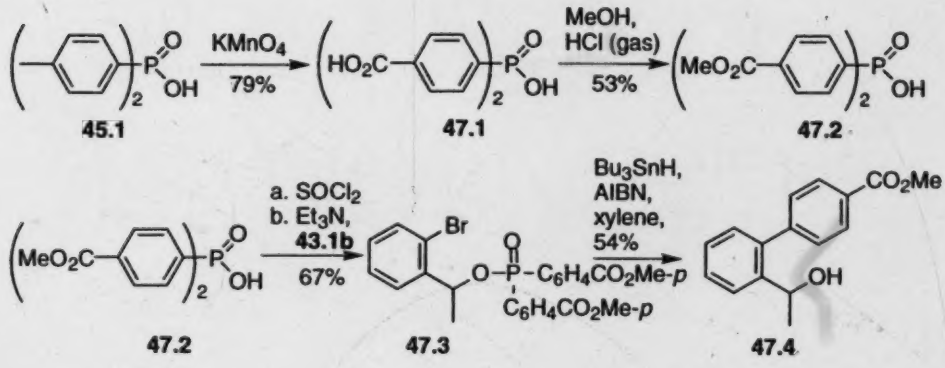


46.1 **46.2** **46.3**

The attempt to make bis(4-methoxyphenyl)phosphinic acid **46.1**, by analogy to the *p*-toluenephosphinic acid **45.1**, failed. Fortunately, the acid **46.1** is commercially available. Again, chlorination with an excess of $SOCl_2$ gave the corresponding acid chloride, and the crude material was used to phosphinylate the benzyl alcohol **43.1b**, producing phosphinate **46.2** as a pale yellow oil in 96%. Stannane and AIBN treatment in xylene gave the rearranged biaryl derivative **46.3** in 52% yield.

From the above two examples, it is seen that electron-donating substituents (Me, OMe) on the migrating aryl ring are tolerated in this type of transformation. We then examined the effect of an electron-withdrawing group, and for this purpose we made compound **47.3**.

Scheme 47



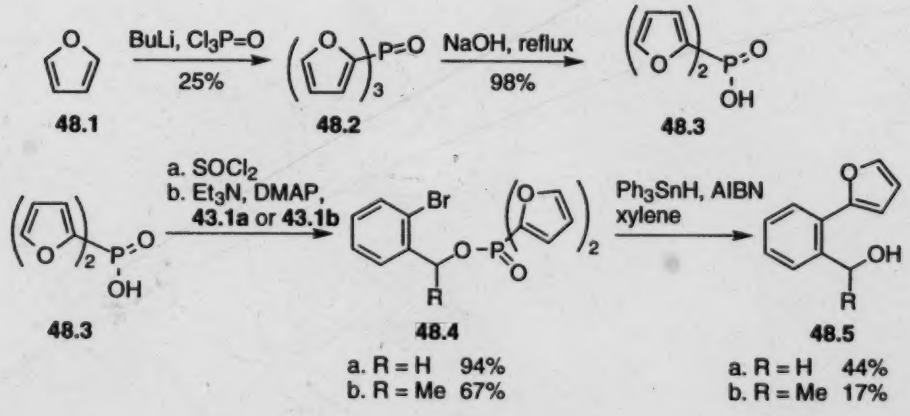
Acid **47.2** was made from *p*-toluenephosphinic acid **45.1** by a literature procedure.[12] In the first step, acid **45.1** was treated with $KMnO_4$ in refluxing aqueous KOH (10%). The carboxylic acid **47.1** was produced in 79% yield. In the second step, the desired acid **47.2** was obtained as a white solid by bubbling HCl gas into a refluxing MeOH solution of **47.1**.

As before, treatment with an excess of $SOCl_2$ gave the corresponding phosphinic chloride, which was used to make phosphinate **47.3** (67% yield), the radical precursor. Application of the standard radical sequence gave the transfer product **47.4** in 54% yield. This result shows that

an electron-withdrawing substituent on the migrating aryl ring is also accommodated.

At this stage we decided to vary the nature of the aromatic ring that undergoes transfer, and we first examined transfer of a furyl group. The desired phosphinic acid **48.3** was made by two steps from furan. Furan was treated with BuLi and then with $POCl_3$ according to a literature procedure,[13] so as to generate compound **48.2**, in low yield (the reported yield in the literature is ca 22%). The desired phosphinic acid **48.3** was obtained as a white solid in

Scheme 48



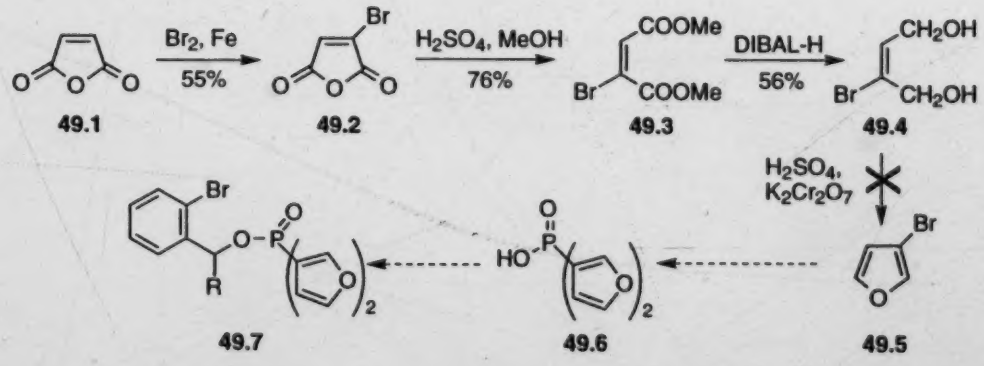
high yield by exposure of **48.2**, to refluxing 10% aqueous NaOH, following the literature procedure.[14]

With phosphinic acid **48.3** in hand, $SOCl_2$ treatment, followed by phosphinylation of the benzyl alcohol **43.1b**, gave radical precursor **48.4b** in 67% yield. Radical transfer and aqueous KF workup gave the desired product **48.5b** in very low

yield (7%). The simple reduction product (replacement of the Br in **48.4b** by H) was isolated in ca 3% yield. No starting material was recovered. Almost the same results were obtained in several repetitions of the experiment, and it is not clear why the desired transformation does not occur efficiently. Then we tried the less hindered benzyl alcohol, **43.1a**. The resulting phosphinate **48.4a** was subjected to the radical transfer conditions, but the desired product was again obtained in low yield (6%). The simple reduction product was isolated in 15% yield, and no starting material was found.

At this point we decided to try the $NaCNBH_4$ workup conditions developed by Crich.[9] To our delight, the yield from **48.4a** to **48.5a** was improved to 44%, although the reduction product was obtained in 19% yield. When we applied these workup conditions to the transformation of **48.4b** into **48.5b**, however, there was no significant improvement, as the yield of **48.5b** was only 17% yield.

Scheme 49



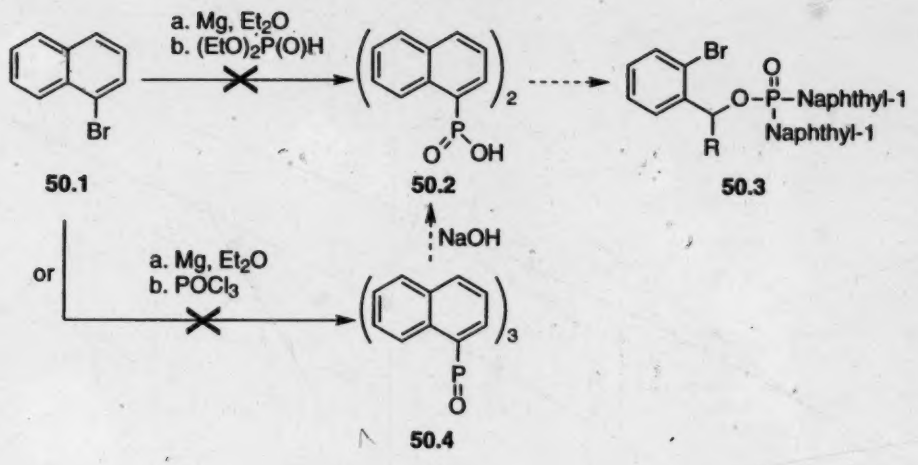
We then tried to test the transfer process, using another furyl-substituted phosphinate.

Our aim was to use **49.7**, which we tried to make along the lines shown in Scheme 49. In order to make the radical precursor **49.7**, the corresponding phosphinic acid **49.6** was, of course, required. Maleic anhydride **49.1** was first converted in four steps into bromide **49.4**. Bromination of anhydride **49.1** with Br_2 in the presence of iron metal[15] gave bromo anhydride **49.2** in 55% yield after purification by vacuum distillation. Diester **49.3** was then produced in 76% yield from anhydride **49.2** by treatment with MeOH in the presence of acid,[16] and diol **49.4** was generated from **49.3** by reduction with DIBAL-H. However, the transformation of diol **49.4** to bromofuran **49.5** by oxidation, according to the literature procedure,[17] failed, and so we were unable to try the subsequent reactions.

We next tried to make the naphthylphosphinate **50.3**, but were unable to convert **50.1** into either **50.2** or **50.4**.

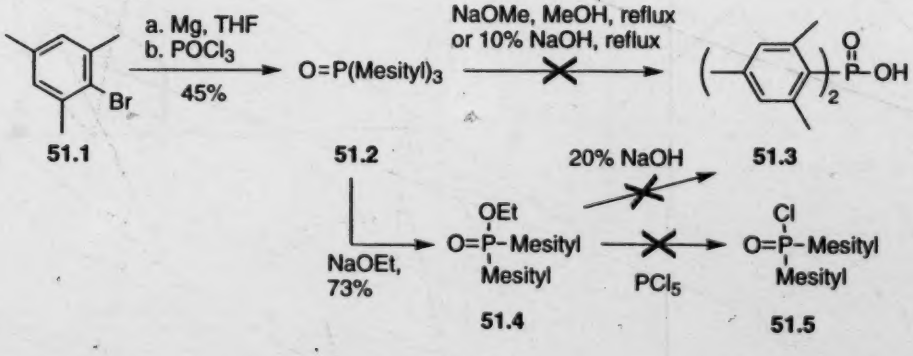
In this case we tried to make the required phosphinic acid by analogy to the *p*-toluenephosphinic acid **45.1**. However none of the desired product **50.2** was obtained. If we could make phosphine oxide **50.4**, the corresponding acid would be obtained by treatment with NaOH, as was done in the case of furylphosphinic acid **48.3**. Although the same procedure used to make furylphosphinic acid **48.3** was followed, the desired trinaphthylphosphine oxide **50.4** was not formed.

Scheme 50



We suspected that the 1-naphthyl functional group is hindered by *peri* interactions, and this contributed to the failure of the reactions we had tried. From Motherwell's series,[18] the hindered trisubstituted phenyl group worked quite nicely, and so we wondered if a similar result would be found with our methodology.

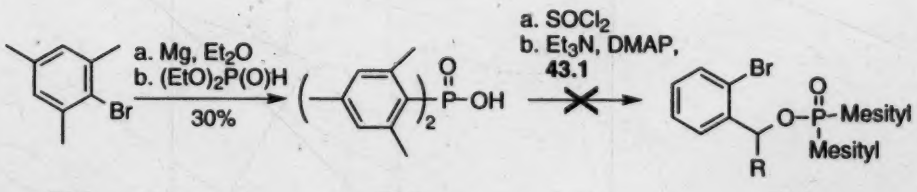
Scheme 51



To test this possibility, we first needed the phosphinic acid **51.3** or phosphinic chloride **51.5**. According to the literature procedure,[19] compound **51.3** could be made from 2-bromomesitylene **51.1** in three steps. Mesitylphosphine oxide was obtained from $POCl_3$ and mesityl Grignard reagent generated from mesityl bromide (**51.1**). However, the desired phosphinic acid **51.3** was not obtained after hydrolysis using refluxing MeONa in MeOH[19] or aqueous NaOH, even though the latter reagent had been used to make the furylphosphinic acid **48.3**.[14] The phosphinate **51.4** was obtained in 73% yield when **51.2** was treated with EtONa. However, phosphinate **51.4** was so stable that the desired hydrolyzed product was not produced even when the compound was treated with boiling aqueous NaOH (20%) or aqueous NaOH in the presence of Bu_4NOH,[20] or with trimethylsilyl chloride in refluxing MeCN.[21] We even tried direct chlorination of **51.4**, using PCl_5,[22] but none of the desired phosphinic chloride was found.

We then tried the method[11] which had allowed us to make the *p*-toluenephosphinic acid **45.1**.

Scheme 52

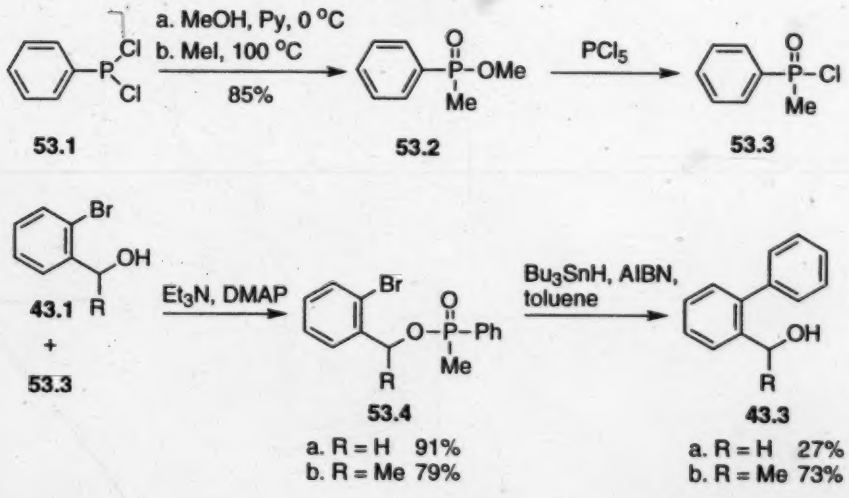


51.1 **51.3** **52.1**

Indeed, the acid **51.3** was obtained from 2-bromomesitylene **51.1** in 30% yield, using this method. However, the radical precursor, phosphinate **52.1**, was not obtained by our routine $SOCl_2$ chlorination and phosphinylation sequence.

We continued exploring the generality of the radical methodology even though we were unable to make some of the starting materials we wanted. In the radical transfer process only one of the two aryl subunits in the diarylphosphinate precursors is transferred. Accordingly, we wondered if a monoarylphosphinate such as **53.4** would give the desired aryl transfer product under our standard conditions.

Scheme 53



To answer this question, the alkylarylphosphinates **53.4** became our next targets. Like the previous examples, the

corresponding phosphinic acid or phosphinic chloride **53.3** are the essential intermediates en route to the phosphinates **53.4**. It turned out to be easier to make the phosphinic chloride **53.3**. This was done in three steps from $PhPCl_2$ (**53.1**), following the literature procedure.[22] Phosphine **53.1** was treated with MeOH in the presence of pyridine. Simple filtration and evaporation gave the crude dimethyl phenylphosphonite, which was used without further purification. The phosphinate **53.2** was produced from this crude dimethyl phenylphosphonite by refluxing for 12 h in iodomethane and gradually raising the temperature to 100 °C as the reaction proceeded. The yield for these two steps was 85%. The pure phosphinate **53.2** was chlorinated with PCl_5 (1 mol per mol of starting material). Filtration and evaporation with protection from moisture gave the crude methyl phenylphosphinic chloride **53.3**, which was used in the next step without further purification.

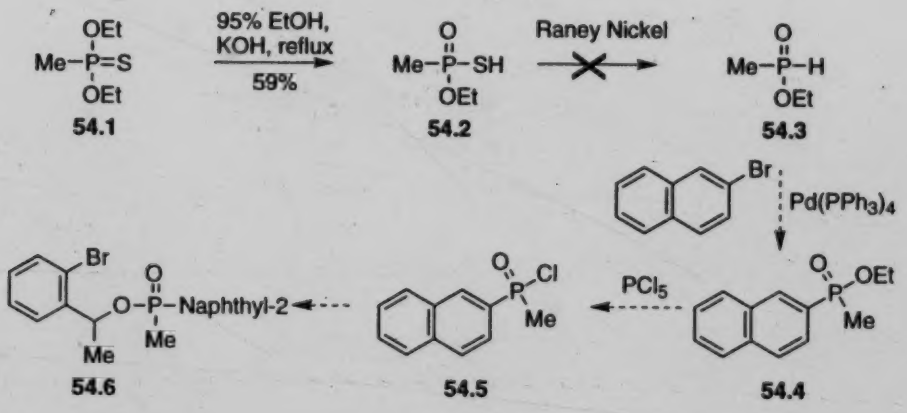
Having the phosphinic chloride in hand, standard phosphinylation of benzyl alcohols **43.1** produced the corresponding phosphinates **53.4** in good yields. Compound **53.4b** was obtained as a mixture of two diastereoisomers. When the phosphinate **53.4a** (R = H) was treated with Ph_3SnH and AIBN in xylene, a low yield (17%) of the desired transfer product **43.3a** was obtained. However, when phosphinate **53.4b** was subjected to treatment with *tributyl*tin hydride and AIBN in PhMe, a high yield (73%) of the desired rearranged product **43.3b** was obtained. When the same conditions were applied to

phosphinate **53.4a**, the yield was slightly better (27%). However, we did not carry out a systematic survey of the relative merits of these two stannanes.

Monoarylphosphinates **53.4** produced the same products as the diarylphosphinates **43.2**, and so we conclude that the alkylarylphosphinates are just as suitable starting materials as diarylphosphinates.

The successful transfer of the phenyl group in the methylphenylphosphinates **53.4** suggested a way of transferring a naphthyl group. This time, compound **54.5** was our new target.

Scheme 54

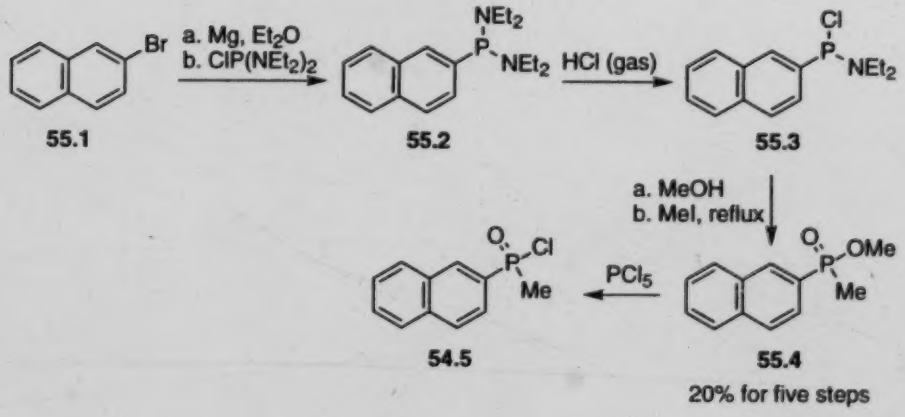


Phosphinate **54.4** is a known compound, which can be made[23] from diethyl methylphosphonothioate **54.1** in three steps. The starting thioate **54.1** was treated with KOH in refluxing 95% EtOH[23a] to give pure **54.2** in 59% after vacuum distillation. However, when the thiophosphinate **54.2** was subjected to desulfurization conditions (Raney nickel in

refluxing *i*-PrOH[23b]) none of the desired methylphosphinate **54.3** was obtained, so that our planned route to the radical precursor **54.6** by palladium catalyzed coupling[23c] and subsequent chlorination and phosphinylation had to be abandoned.

In order to obtain compound **54.6**, we had to explore another route to phosphinate **55.4** (Scheme 55), which was similar to the one used for making **53.2**.

Scheme 55

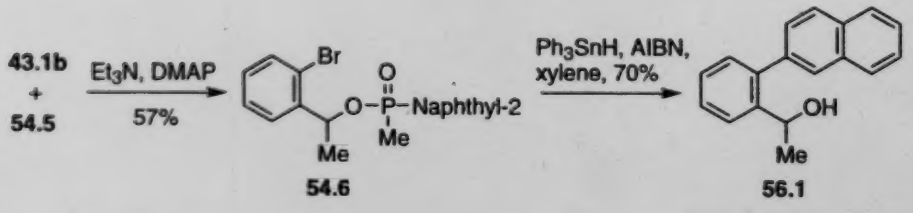


In this route, we needed the starting dichloronaphthylphosphine, corresponding to **53.1**, in order to follow all the steps we had used for making methylphenylphosphinic chloride **53.3**. Fortunately, the dichloronaphthylphosphine is known and it can be made[24] from 2-bromonaphthalene. This time, based on our failure to make bisnaphthylphosphinic acid **50.2**, we used 2-bromonaphthalene, so that we could operate at the less hindered β-position. The required reagent,

chlorobis(diethylamino)phosphine was made[24] from PCl_3 and Et_2NH in a 1:4 ratio, since 2 equiv. of amine are sacrificed by combination with HCl produced from the reaction. The pure chlorobis(diethylamino)phosphine was treated with 2-naphthylmagnesium bromide to generate the naphthylphosphine **55.2**, which was then treated with HCl gas. However, we isolated compound **55.3** instead of the desired dichloronaphthylphosphine, as judged by ^1H NMR analysis.

After a careful consideration of the conversion of **53.1** into **53.2**, in which pyridine was required, we realized that the monochloronaphthylphosphine **55.3** might serve just as well as the expected dichloro compound, and a base (pyridine) might not be needed since Et_2NH would be produced from the reaction and would perform the role of pyridine. To our delight, after treatment with MeOH and MeI, the desired pure phosphinate **55.4** was obtained. The yield was 20% for the 5 steps from the starting 2-bromonaphthalene. Phosphinate **55.4** was chlorinated with PCl_5 to give crude phosphinic chloride **54.5**, which was used in the next step without further purification.

Scheme 56



Having the methylnaphthylphosphinic chloride in hand, phosphinylation gave a mixture of two diastereoisomers of the radical precursor **54.6** in a total yield of 57%. Small amounts of the individual isomers were obtained by chromatography. The individual isomers and the mixture of the two were each subjected to the radical transfer conditions producing the same desired naphthyl transfer product **56.1**, and the yields were almost the same (70%) in each case. This result showed that the stereochemistry of the starting material had no effect on the reaction, and we had at last succeeded in transferring a naphthyl group.

Variation of the parent alcohol

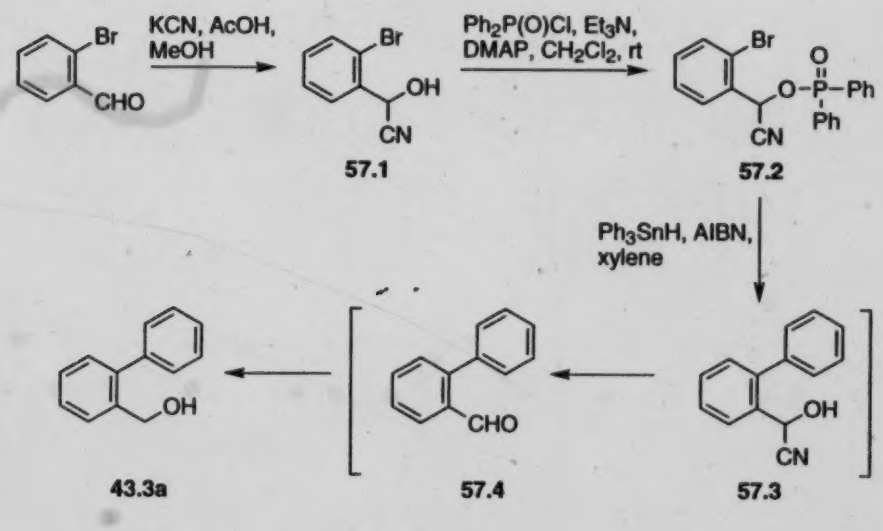
In this section, a detailed study of the accepting aryl unit will be discussed. We examined different substituents in the aromatic ring, different types of aromatic rings, and also the possibility of using an alkyl group instead of an aromatic unit.

First of all, we made changes to the R substituent in phosphinate **43.2** by using a cyano substituent, as in **57.2** and in the enol derivatives **58.3** and **59.2** (see later).

The cyanohydrin **57.1** was generated in 81% yield from 2-bromobenzaldehyde[25] by treatment with KCN in the presence of acetic acid. Routine phosphinylation with commercially available $Ph_2P(O)Cl$ produced the radical precursor **57.2** as thick, yellow oil in 90% yield. However, the standard radical conditions gave compound **43.3a** in 28% yield instead

of **57.3**. In addition, the dehalogenated product (Br replaced by H in **57.2**) was isolated in 13% yield. In this sequence,

Scheme 57



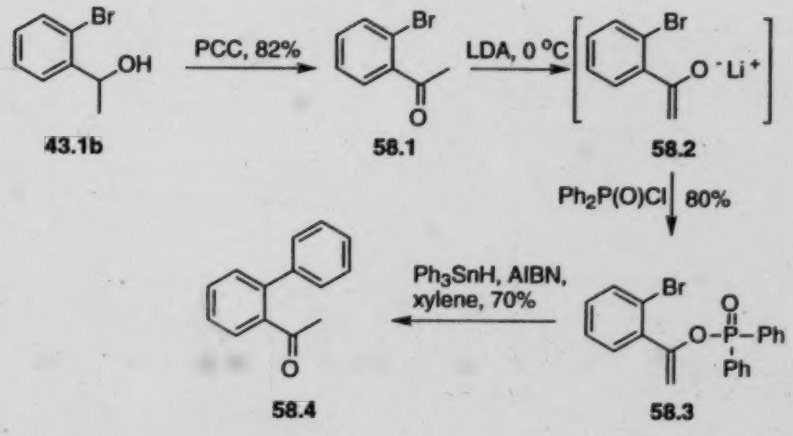
the intermediate cyanohydrin derivative **57.3** evidently lost HCN to afford the corresponding aldehyde **57.4**, which was reduced further by stannane to give **43.3a**, the product actually isolated. Indeed, aldehyde **57.4**, made independently, can be reduced by stannane to generate alcohol **43.3a** (90%).

In the previous examples, we used simple alcohols as starting materials for phosphinylation with a phosphorus reagent.

We next tried to make an enol phosphinate, e.g. **58.3**, using the corresponding lithium enolate **58.2** as the starting material for the phosphinylation.

Oxidation of alcohol **43.1b** with PCC gave ketone **58.1** in 82% yield. The ketone was converted into its enolate by treatment with LDA at -78 °C for 1 h, and then phosphinylation *in*

Scheme 58



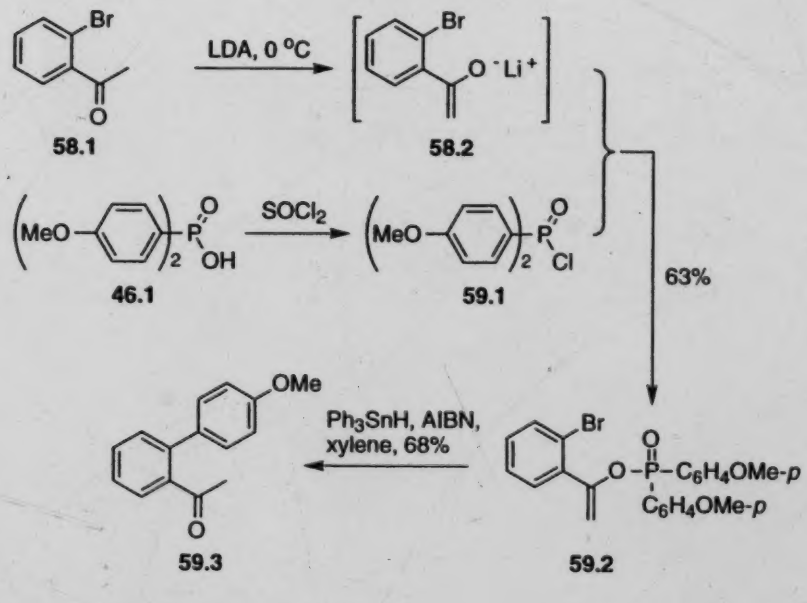
situ with $Ph_2P(O)Cl$ gave the desired enol phosphinate, but the yield was only about 12%. Since 62% of the starting ketone **58.1** was recovered, it was suspected that the reaction temperature (-78 °C) was too low. When the temperature was raised to 0 °C, a much better yield (80%) was obtained. With the enol phosphinate **58.3** in hand, standard radical transfer conditions afforded the desired aryl transfer product **58.4**, in which the ketone functional group remained rather than being reduced by stannane, as was the case with aldehyde **57.4**.

In order to establish if the transfer from enol derivatives is general, we made another enol phosphinate

(**59.2**), using bis(*p*-methoxyphenyl)phosphinic chloride **59.1**.

The lithium enolate **58.2**, generated from ketone **58.1** by treatment with LDA, was allowed to react with crude phosphinic chloride **59.1**. The latter was made from the

Scheme 59



corresponding phosphinic acid **46.1** by chlorination with $SOCl_2$. The enol phosphinate **59.2** was obtained in 63% yield. Under our standard radical conditions, the desired biaryl ketone was formed in good yield (68%).

In these two cases, the radical aryl transfer occurred very smoothly.

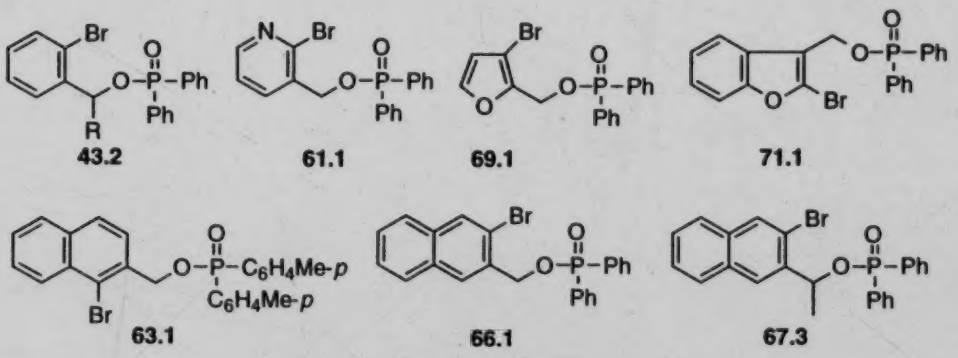
The next modification we made was to change the accepting aromatic unit from a normal benzene ring (as in **43.2**) to a pyridine (**61.1**), a naphthalene (**63.1**, **66.1** and

67.3), a furan (**69.1**), or a benzofuran (**71.1**) (see Figure 1).

We first made the pyridine alcohol **60.4** in three steps, following the literature procedure.[26] Commercial amine **60.1** was treated[26a] with $NaNO_2$ and Br_2 in the presence of HBr,

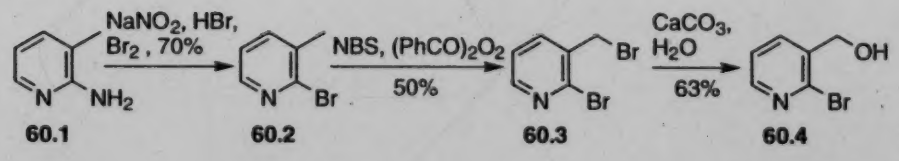
Figure 1

Structures of potential transfer starting materials



producing 2-bromo-3-methylpyridine **60.2** in 70% yield. Bromination[26b] with NBS in the presence of a catalytic amount of $(PhCO)_2O_2$ gave 2-bromo-3-(bromomethyl)-pyridine **60.3** in 50% yield. Hydrolysis,[26b] using water and $CaCO_3$ in refluxing 1,4-dioxane, then produced the desired 2-bromo-3-pyridine-

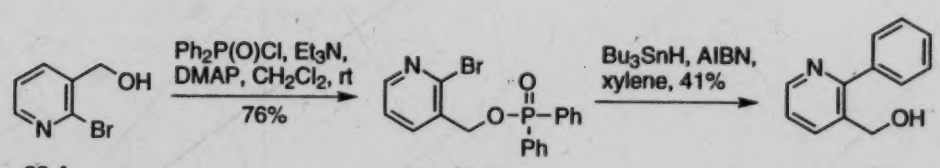
Scheme 60



methanol **60.4**.

Phosphinylation of **60.4** with commercial $Ph_2P(O)Cl$ in the presence of Et_3N gave the radical transfer precursor **61.1** as a white solid, and, under the radical conditions, the desired phenyl transfer product **61.2** was formed in 41% yield. When Ph_3SnH was used, a slightly lower yield was obtained (36%). A lower-boiling point hydrocarbon (PhMe in this case) was also tried as the solvent, but then the yield was only 16% (Ph_3SnH was used).

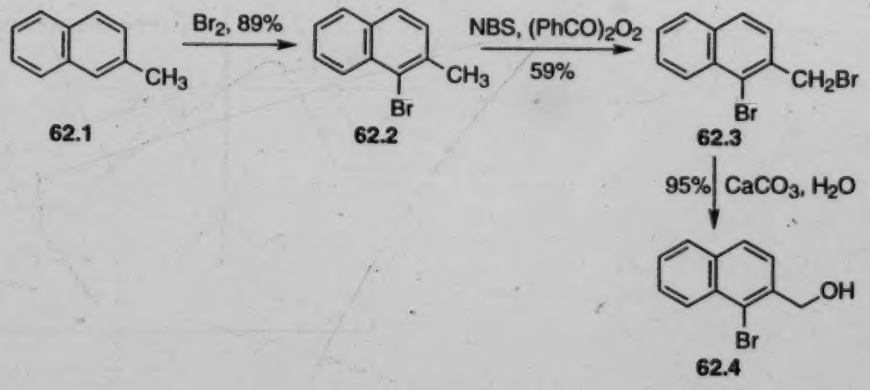
Scheme 61



60.4 **61.1** **61.2**

We next attempted to use a naphthalene as the accepting aromatic unit.

Scheme 62

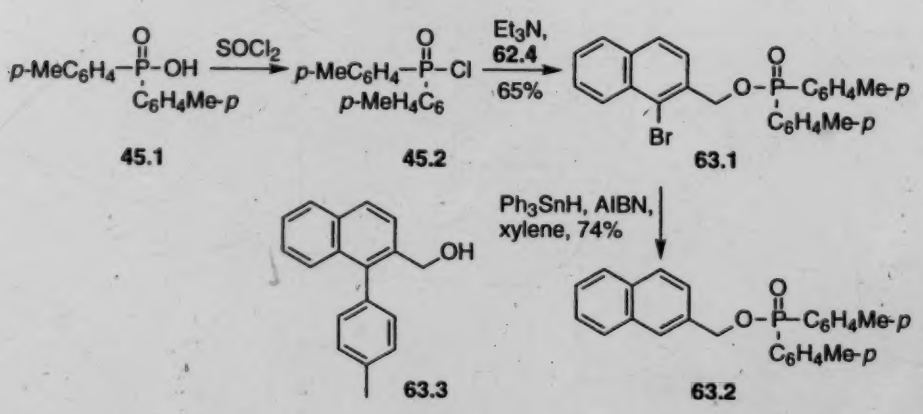


62.1 **62.2** **62.3** **62.4**

Naphthyl alcohol **62.4** was made from 2-methylnaphthalene (**62.1**) in three steps. Bromination[27] at the α-position with Br_2 gave 1-bromo-2-methylnaphthlene (**62.2**) in 89% yield. A second bromination[26b] at the benzylic position, this time with NBS in the presence of catalytic amount of $(PhCO)_2O_2$, generated bromonaphthalene **62.3**, and this was hydrolyzed[26b] to produce the desired 1-bromo-2-naphthalenemethanol **62.4**.

The naphthalene alcohol **62.4** was treated with crude bis(*p*-toluene)phosphinic chloride **45.2**, generated from the corresponding acid **45.1** by chlorination with $SOCl_2$, and the phosphinate **63.1** was obtained in 65% yield. To our disappointment, on treatment with Ph_3SnH, the simple reduction product **63.2** (replacement of Br by H) was obtained in 74% yield, and none of the desired aryl transfer product **63.3** was observed.

Scheme 63

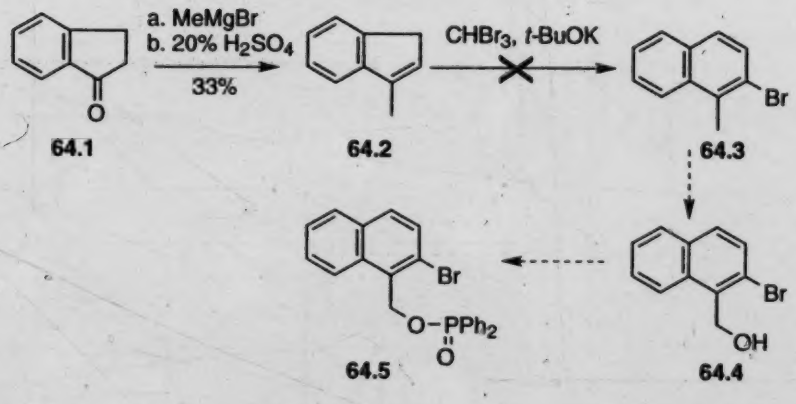


Possibly, *peri* interactions hinder the desired process in this case. We therefore wanted to examine compound **64.5**

where such *peri* interactions would not play a detrimental role.

For this purpose, alcohol **64.4** is the key compound to make, and this should be available from 2-bromo-1-methylnaph-

Scheme 64

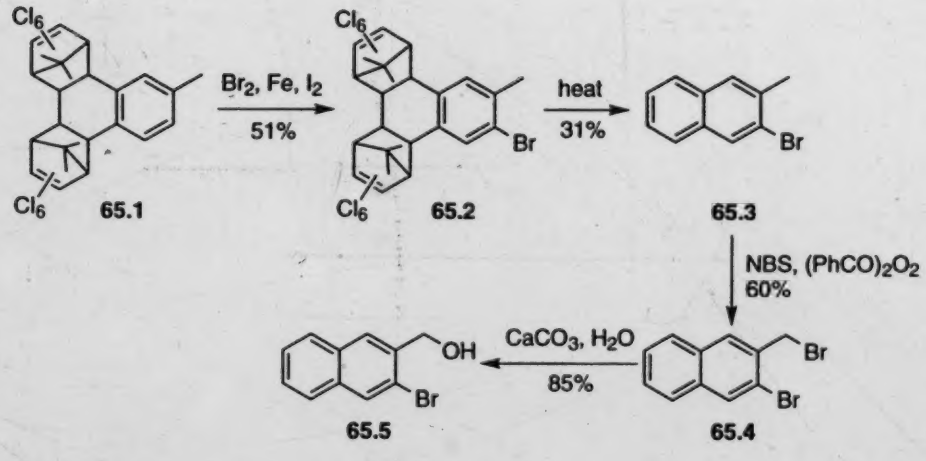


thalene **64.3**, using bromination with NBS and hydrolysis with $CaCO_3$-H_2O (cf. **62.2→62.4**). However, our attempts at making compound **64.3** were unsuccessful, even though a literature procedure[28] for the conversion of **64.1** to **64.3** was followed. The first step from 1-indanone (**64.1**) to 1-methylindene **64.2** proceeded by methylation with a Grignard reagent and subsequent dehydration with refluxing H_2SO_4 (20%). In the second step, methylindene **64.2** was treated with dibromocarbene, generated *in situ* from $CHBr_3$ and *t*-BuOK, but this reaction gave a complex mixture, and none of the desired 2-bromo-1-methylnaphthlene (**64.3**) was found. Therefore we had to seek another model compound, and compound **65.5** was

chosen as a suitable parent alcohol.

The desired bromoalcohol **65.5** was produced from 2-bromo-3-methylnaphthalene (**65.3**) by our usual bromination-hydrolysis sequence.[26b] Bromination[29] of the starting bis(hexachlorocyclopentadiene) adduct (**65.1**) of 2-methylnaph-

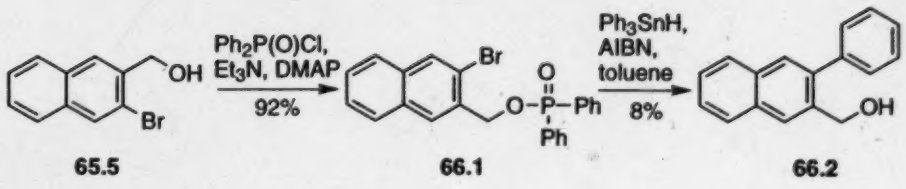
Scheme 65



thalene gave bromo adduct **65.2** in 51% yield. The retro Diels-Alder product obtained by heating **65.2** gave 2-bromo-3-methylnaphthalene (**65.3**) in 31%. This process was not very convenient since the product **65.3** had to be distilled out of the mixture under vacuum while the starting material **65.2** was heated by a Bunsen burner. Indeed the reaction flask and stirring bar were destroyed in each experiment, as the flask residue could never be removed. After this step, the subsequent reactions occurred smoothly.

The usual phosphinylation with $Ph_2P(O)Cl$ in the presence

Scheme 66

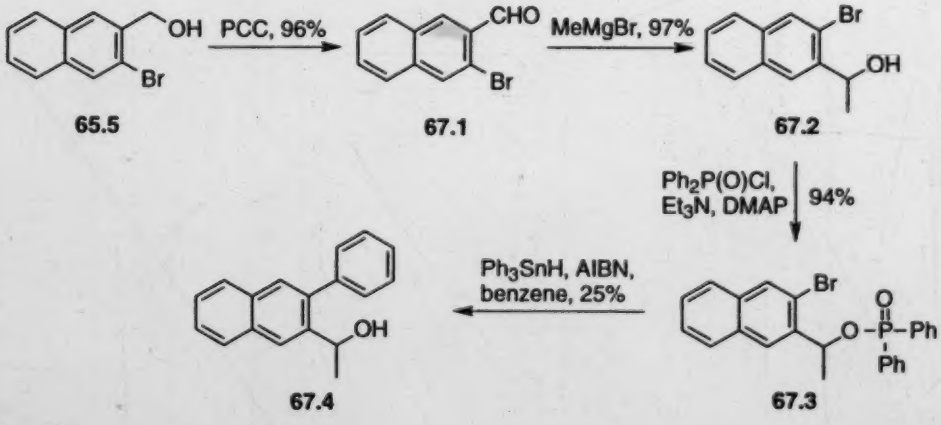


65.5 66.1 66.2

of Et_3N and DMAP gave the corresponding phosphinate **66.1** in 92% yield. To our disappointment, the desired aryl transfer product **66.2** was formed in only 8% yield.

In the case of methylphenylphosphinates **53.4**, the transfer from **53.4b** with a methyl group in the parent alcohol was much more efficient than conversion from **53.4a** without a methyl substituent. We wondered if the transfer might work better if we used **67.2**, in which a methyl substituent is present. Alcohol **67.2** was easily made by PCC oxidation of **65.5** and methylation with MeMgBr. Phosphinylation with

Scheme 67



65.5 67.1 67.2 67.3 67.4

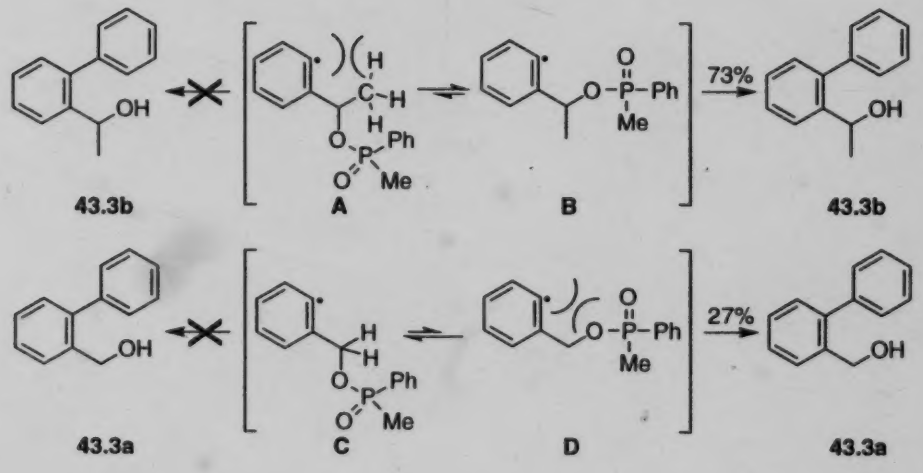
$Ph_2P(O)Cl$ gave the phosphinate **67.3** in 94% yield.

The radical transfer experiment did indeed give a better yield [25% for **67.3** (PhH as solvent) versus 8% for **66.1** (PhMe as solvent] of the desired transfer product, using Ph_3SnH and AIBN. However, we did not determine if the change in solvent was responsible for the improvement. We also tried Ph_3SnH in xylene, which gave 20% of **67.4** and 32% of the dehalogenated product (replacement of Br by H in **67.3**).

In these two transformations (**53.4a→43.3a** versus **53.4b→43.3b**; **66.1→66.2** versus **67.3→67.4**), better yields were obtained from the phosphinates with a methyl group on the accepting aryl unit. These observations may be explained by the Thorpe-Ingold effect (Figure 2). Aryl transfers in intermediates **A** and **C** cannot proceed, but intermediates **B** and **D** can lead to the aryl transfer product **43.3**. For compound

Figure 2

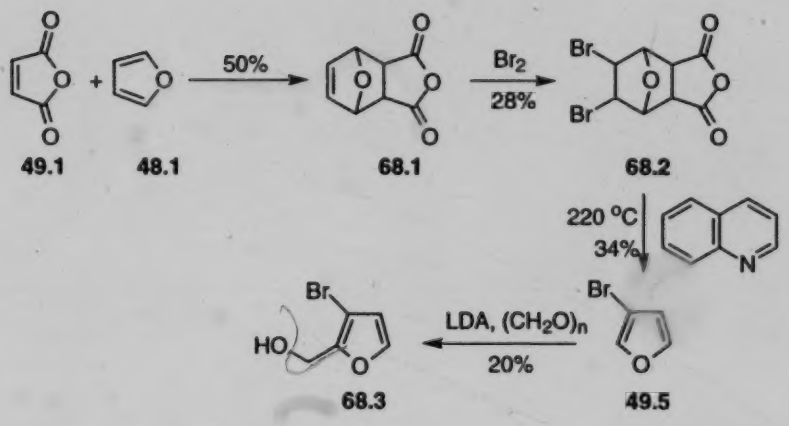
Thorpe-Ingold effect



53.4b, radical **B** is favored as less hindrance is incurred, and consequently a higher yield (73%) of the transfer product **43.3b** is observed. On the other hand, for compound **53.4a**, radical **C** is favored since **D** is relatively sterically hindered in this case, and consequently a low yield (27%) is obtained.

Our next target was compound **68.3** and, after some exploratory experiments (see Scheme 49), we designed a convenient route to this substance.

Scheme 68

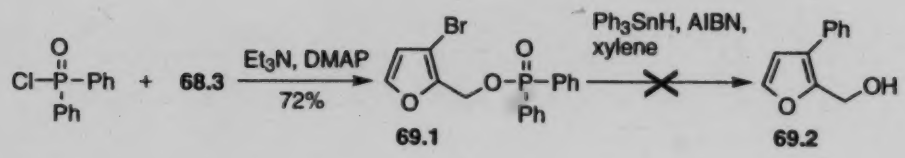


Diels-Alder reaction[30] of maleic anhydride and furan generated adduct **68.1**, and the dibromo compound **68.2**, made by treatment with Br_2,[31] was converted[32] to bromofuran **49.5** by heating at 220 °C with quinoline. We had earlier tried to make **49.5** as a precursor to **49.7**, but we decided not to reinvestigate the preparation of **49.7**, and instead we used the present material to make **69.1**. The required parent

alcohol **68.3** was produced from bromofuran **49.5** by reaction with LDA and formaldehyde.[33]

The alcohol was then phosphinylated to produce phosphinate **69.1** in 72%. However, none of the desired aryl transfer product **69.2** was observed under the standard radical

Scheme 69

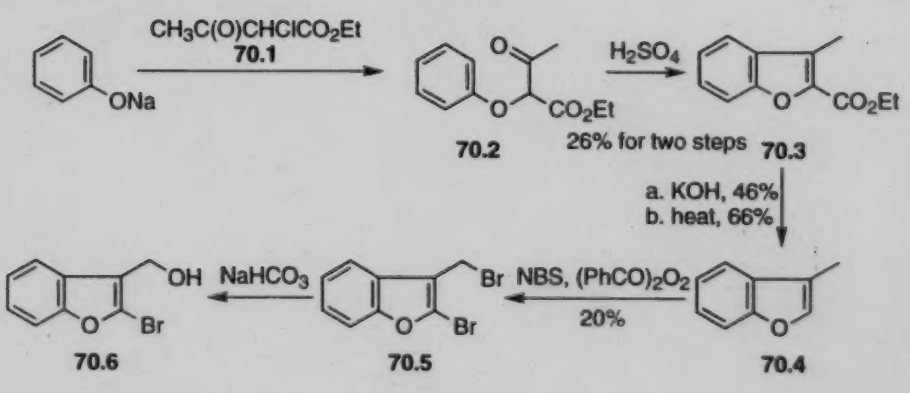


conditions, and only a small amount (ca 2%) of starting phosphinate **69.1** was recovered.

One further attempt was made to effect transfer to a furan unit, and in this case the benzofuryl alcohol **70.6** was used.

3-Methylbenzofuran (**70.4**) was made from phenol and ethyl

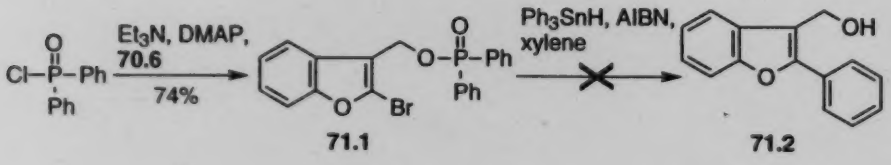
Scheme 70



acetoacetate by the literature procedure.[34] Ethyl chloroacetoacetate (**70.1**) was generated (88%) from ethyl acetoacetate by treatment with SO_2Cl_2. The reaction of chloroacetoacetate **70.1** and sodium phenolate gave acetoacetate **70.2**. The crude material was treated with H_2SO_4 to produce benzofuran **70.3**. Hydrolysis with KOH and decarboxylation by heating to 280 °C gave 3-methylbenzofuran **70.4**. Double bromination[35] of **70.4** with 2 equiv. of NBS in the presence of a catalytic amount of $(PhCO)_2O_2$ yielded the dibromo compound **70.5**, and the desired alcohol **70.6** was obtained by hydrolysis with $NaHCO_3$-water in refluxing 1,4-dioxane.

The usual phosphinylation of compound **70.6**, with $Ph_2P(O)Cl$, generated phosphinate **71.1** in 74% yield. However, under our radical conditions (Ph_3SnH, AIBN, xylene), an unidentified product was obtained, and no transfer product was found. It is not clear why transfer to a furan unit does not work.

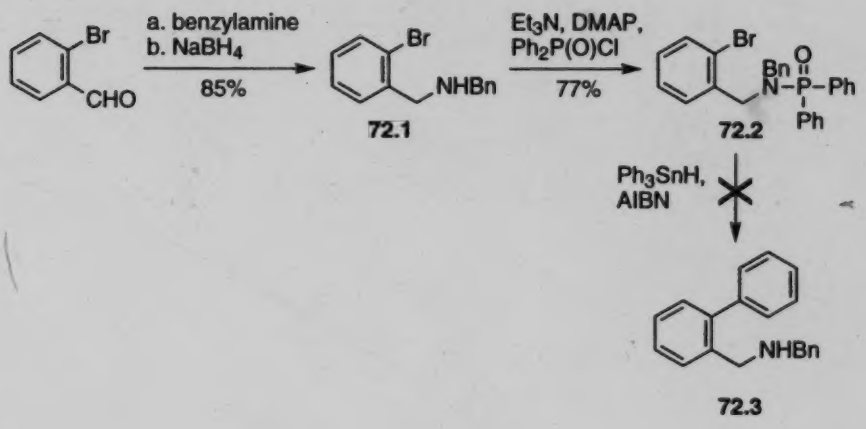
Scheme 71



We next examined the possibility of using nitrogen as a linking atom, so as to establish whether the aryl transfer might occur in phosphinamides.

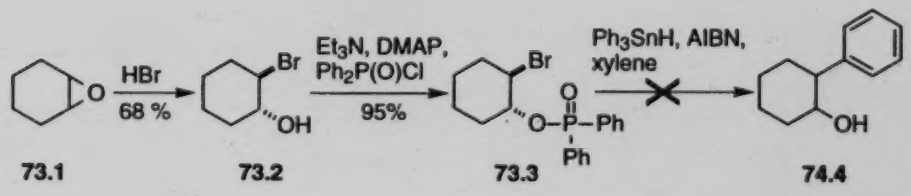
o-Bromobenzaldehyde was converted into *N*-benzyl-*o*-bromobenzylamine **72.1** by treatment with benzylamine and sodium borohydride.[36] Then the radical precursor, phosphinamide **72.2**, was obtained in 77% yield by the usual phosphinylation process. However, treatment with a stannane gave a complex mixture, and no transfer product was found.

Scheme 72



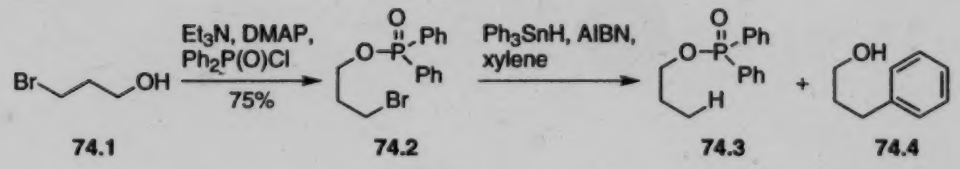
All of the aryl transfer reactions discussed involved transfer or attempted transfer to an aryl radical, and so the question arose as to whether transfer to an alkyl radical was possible.

Scheme 73



Cyclohexene oxide was converted[37] into 2-bromocyclohexanol (**73.2**) by the action of HBr, and phosphinylation then gave phosphinate **73.3** as a white solid in 95% yield. Stannane addition produced a complex mixture of unidentified products. In this case, the alkyl radical generated from the stannane addition would have to undergo a 5-*exo* cyclization, whereas all our successful examples involve a 6-*exo* process.

Scheme 74



74.1 **74.2** **74.3** **74.4**

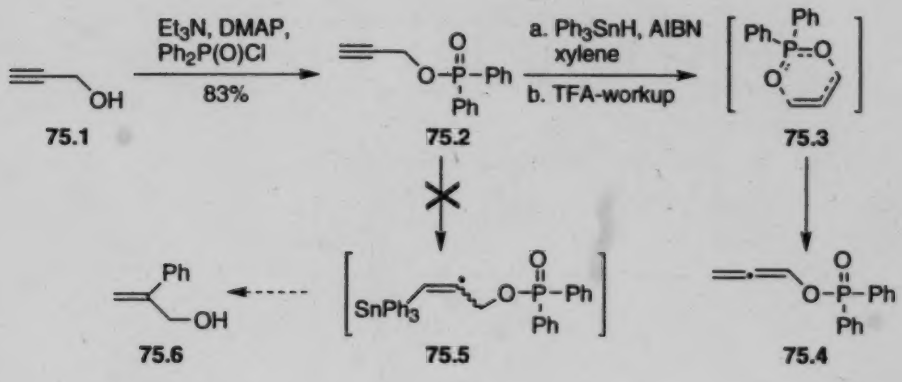
For this reason, we also studied the possible conversion of **74.2** into **74.4**, where the normal 6-*exo* cyclization would be involved. The primary alkyl radical derived from phosphinate **74.2** gave an inseparable mixture of reduced product **74.3** and transfer product **74.4**. From the ^{1}H NMR spectrum of the crude material, the reduced product was the major component (ca 2:1), and we can conclude that alkyl radicals are less suitable for the aryl transfer.

Lastly, we examined transfer to a vinyl radical (**75.5**). This was generated from alkyne **75.2**, and the intermediate radical would have to undergo a 5-*exo* cyclization.

Propargyl alcohol **75.1** was converted into phosphinate

75.2 by phosphinylation with $Ph_2P(O)Cl$. After treatment with Ph_3SnH, the product actually isolated was the allenic compound **75.4**, and, in fact, compound **75.4** was also obtained just by refluxing **75.2** in xylene. Presumably, the six-membered transition state **75.3** is involved.

Scheme 75

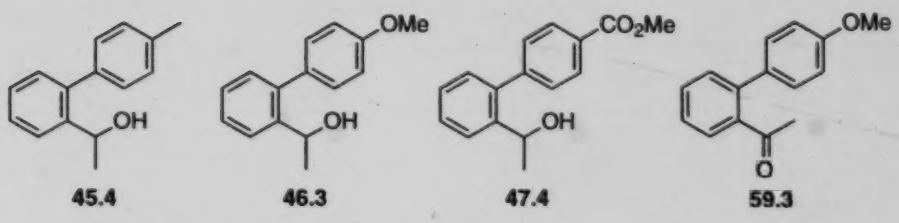


Mechanistic studies

The expected mechanism of the radical rearrangement for the case of **43.2b→43.3b** is summarized in Scheme 76, and is supported by experimental evidence.

Figure 3

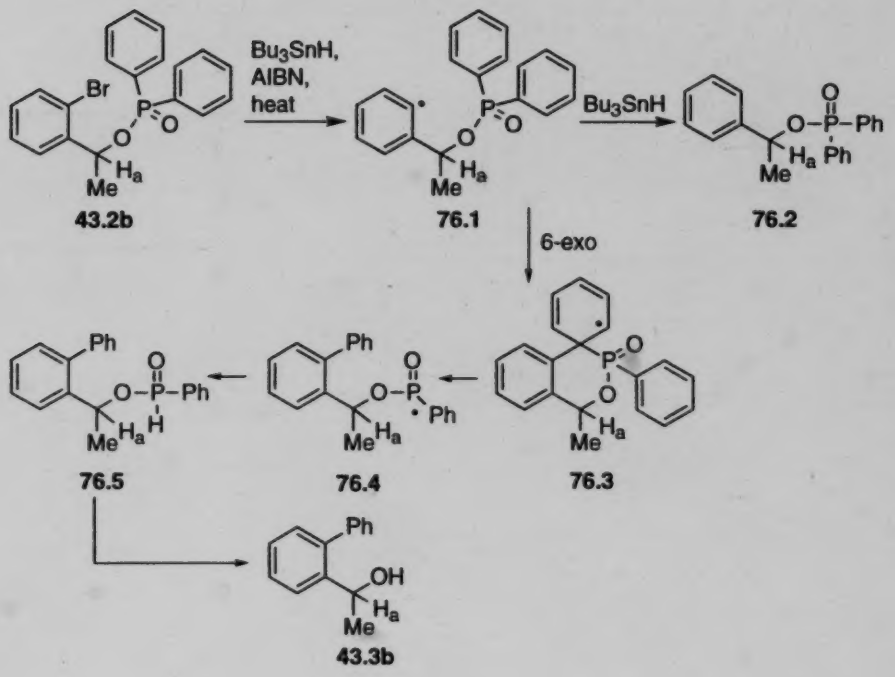
***para*-Substituted transfer products**



The *ipso* nature of the initial radical attack (see **76.1→76.3**) follows from examination of those cases (**45.3→45.4**, **46.2→46.3**, **47.3→47.4**, **59.2→59.3**) where the substituent on the migrating ring serves as a marker.

Therefore, it is reasonable to assume that the early stages of the reaction involve the steps shown in Scheme 76,

Scheme 76



with the initial radical transfer occurring via a six-membered transition state. The stannane/AIBN mediated free radical abstraction of Br in **43.2b** generates aromatic radical **76.1**. This then undergoes intramolecular *ipso* attack on the aromatic ring adjacent to the phosphorus, forming the

spirocyclohexadienyl radical **76.3**. Rearomatization of **76.3** by expulsion of the phosphorus unit, and subsequent hydrogen abstraction gives **76.5**. However, we have not established the mechanism by which **43.3b** is finally liberated. In this process, simple hydrogen abstraction by radical **76.1** gives the reduced product **76.2**. This reduction competes with the aryl transfer. The intermediacy of phosphinate **76.5** (at least on one pathway) was confirmed by isolation and comparison with an authentic sample, and by following the reaction spectroscopically, as follows.

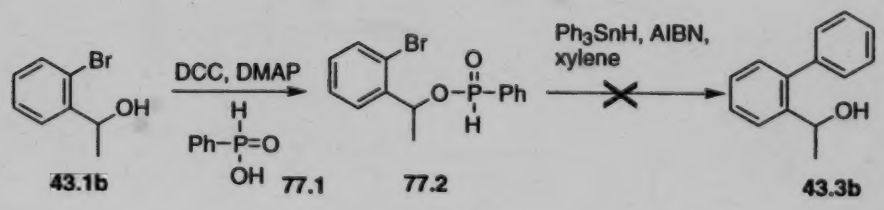
When the rearrangement of **43.2b** in PhMe was monitored by ^{1}H NMR, a clear sequence of changes was observed. The NMR spectra were measured after the addition of 0.5, 1.0, 1.5, and 2.0 mol Ph_3SnH per mol of **43.2b**. The signal corresponding to H_a (see Scheme 76 above) in the starting material **43.2b** – a multiplet centered at δ 5.84 – decayed, and was replaced by multiplets centered at δ 5.04, 5.50, 5.74, and 5.47. The pair of multiplets at δ 5.50 and 5.74 represent H_a of **76.5** (two diastereoisomers), the multiplet at δ 5.04 is characteristic of H_a in the final product **43.3b**, and the multiplet at δ 5.47 represents H_a of the simple reduction product[38] **76.2**. After the addition of 0.5 or 1.0 equiv. of stannane, all four species, starting material **43.2b**, final product **43.3b**, intermediate phosphinate **76.5**, and reduction product **76.2**, were present. When 1.5 equiv. had been added, all of **43.2b** had reacted; **43.3b**, **76.5**, and **76.2** were present. When 2.0 equiv. had been added, **76.5** was

absent but, of course, the signals for **43.3b** and **76.2** remained. These observations are consistent with the sequence **43.2b**→**76.1**→**76.3**→**76.4**→**76.5**→**43.3b**, and the simultaneous operation of a competitive process **43.2b**→**76.1**→**76.2**, but do not identify the mechanism(s) by which **76.5** (or **76.4**) affords the observed alcohol **43.3b**.

Samples from the same ^{1}H NMR experiment were also examined by ^{31}P NMR, and signals for the starting material **43.2b** (δ 31.5), for the intermediate **76.5**, which exists as two diastereoisomers (δ 22.5 and 23.0), and for the reduction product **76.2** (δ 31.2) were monitored. We observed exactly the same sequence as with the ^{1}H NMR spectra. Thus, the intermediate **76.5** was still present after addition of 1.5 equiv. Ph_3SnH, but had disappeared after addition of 2.0 equiv. We did not observe a ^{31}P signal at δ 23, which would be characteristic[39] of PhPH(O)OH, the expected hydrolysis product of **76.5**.

We next made **77.2**, using phenylphosphinic acid[40] **77.1** and alcohol **43.1b**. We hoped **77.2** would give transfer product **43.3b**, but, under the radical transfer conditions, a

Scheme 77

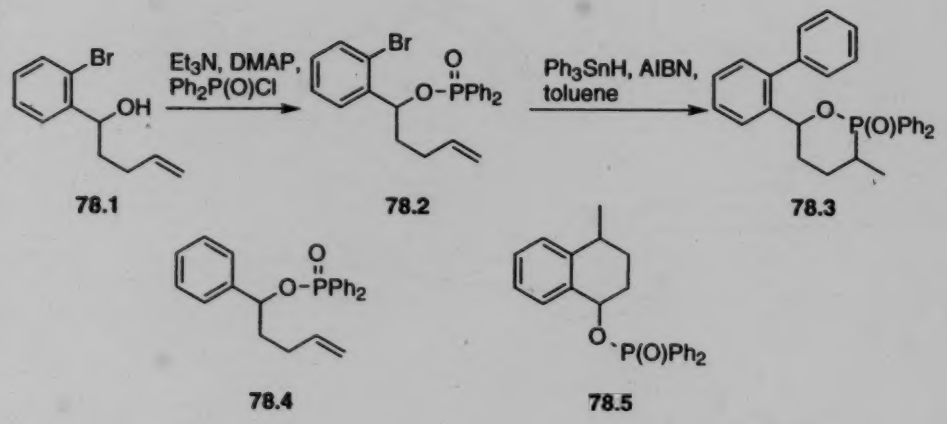


43.1b **77.1** **77.2** **43.3b**

complex mixture was obtained.

We tried to trap the proposed phosphorus radical of type **76.4** involved in the transfer, by using an intramolecular radical trap. Phosphinate **78.2**, made from alcohol **78.1** by phosphinylation with $Ph_2P(O)Cl$, would constitute a suitable test compound, and we hoped it would lead to **78.3**. However, under the standard radical conditions, an inseparable mixture was obtained. The individual spectra of compounds **78.4** and **78.5**, made independently, allowed us to deduce that both these compounds were present in the mixture, but no evidence could be found that the desired **78.3** had been formed.

Scheme 78

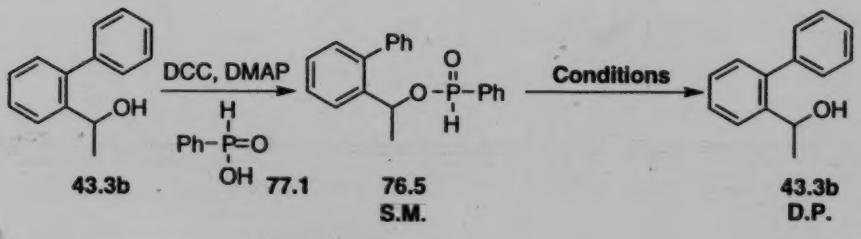


At the beginning of this work we suspected that the isolated alcohol is formed by simple hydrolysis during workup, and this view prompted the use of methanolic K_2CO_3 in the early experiments (see Table 1). However, such a pathway

is ruled out by the subsequent NMR experiments, which show that the final alcohol is present before workup.

An authentic sample of **76.5**, made from phenylphosphinic acid **77.1** and alcohol **43.3b**, was found to be stable to the aqueous KF workup conditions and column chromatography over silica gel. On heating in xylene overnight, **76.5** affords

Scheme 79



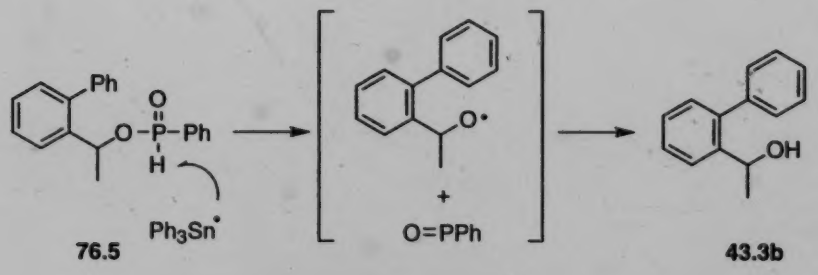
Conditions	
KF-water	S.M.
xylene, reflux	42% D.P.
benzene, reflux	S.M.
toluene, reflux	S.M.
Bu_3SnH, AIBN, benzene, reflux	46% D.P. + 30% S. M.
Ph_3SnH, AIBN, xylene, reflux	48% D.P.
Bu_3SnCl, benzene, reflux	S.M.
EtOH, reflux	S.M.

alcohol **43.3b** (ca 42%), which can be detected (TLC) before workup. In refluxing PhH or PhMe (ca 12 h), **76.5** is stable but gives **43.3b** (ca 46%) in PhH (PhMe was not tested) in the presence of Bu_3SnH and AIBN (30% of starting phosphinate **76.5** remained). On the other hand, **76.5** was completely converted into **43.3b** with Ph_3SnH in refluxing xylene. Heating of **76.5** in PhH overnight in the presence of a large excess (24

equiv.) of Bu_3SnCl or in EtOH (without any additive) resulted in no change.

Finally, we attempted to trap *p*-$MeOC_6H_4P{=}O$,[41] a possible byproduct from the radical transfer reaction in, for example, conversion of **46.2** to **46.3**. This was tried by stirring the reaction mixture with H_2O_2 for a couple hours at room temperature before the KF-water workup. We also attempted to extract any phosphinic acid produced from the reaction, by using Na_2CO_3, but both experiments were unsuccessful.

Scheme 80



Conditions

Ph_3SnH, AIBN, EtOH, reflux
Ph_3SnH, AIBN, xylene, 8-folds of $CH_2{=}CHCOOMe$, reflux
Ph_3SnH, AIBN, xylene, 8-folds of $CH_2{=}CHCN$, reflux
PhC(O)C(O)Ph, xylene, reflux

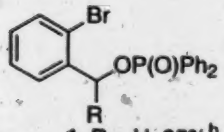
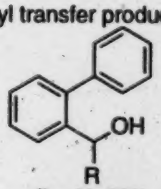
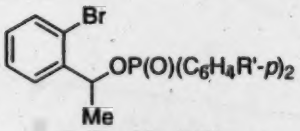
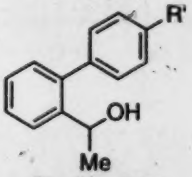
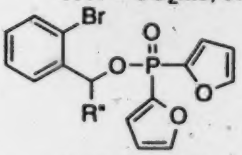
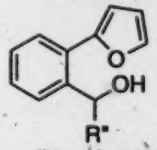
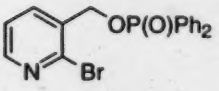
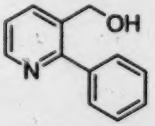
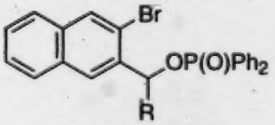
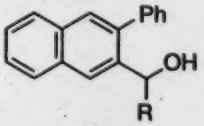
The attempts to trap PhP=O, a possible byproduct in the thermal release of **43.3b** from **76.5**, using EtOH, methyl acrylate, acrylonitrile in the presence either of stannane or benzil[42] in refluxing xylene were unsuccessful, and we did not make any further attempts to identify the later stages of the mechanistic pathway(s).

Conclusion

Our results show that phosphinates can be used for the preparation of biaryls by intramolecular radical aryl transfer. We have studied a number of examples and have established the generality of the process (Table 1), as well as part of the mechanism. The transferred aryl group can be a benzene, substituted benzene, furan or naphthalene ring; the accepting aromatic unit can be a benzene, naphthalene, or pyridine unit. The average yield for 17 examples is 50%; in some cases yields of about 70% are obtained, and the reaction appears to work especially well with enol phosphinates (at least as judged by the two examples studied), giving biaryl ketones. It was established that electron-withdrawing or electron-donating groups on the migrating aryl ring are tolerated, and that alkylarylphosphinates are just as suitable as diarylphosphinates. However, we found that alkyl radicals are not satisfactory in this type of transformation. The present experiments extend the range of available linkers (see Introduction) between aryl groups that can be joined by intramolecular *ipso* radical transfer.

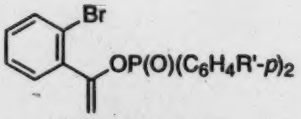
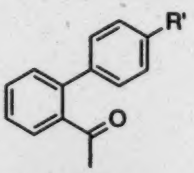
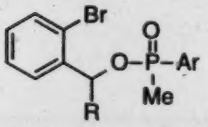
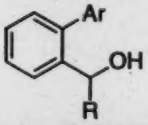
Table 1

Aryl transfer products

Starting phosphinate	Aryl transfer product	Conditions[a]
		
1. R = H, 85%[b]	R = H, 58%	Ph_3SnH,xylene[c]
2. R = Me, 88%	R = Me, 64%	Ph_3SnH, xylene[c]
3. R = Ph, 59%	R = Ph, 46%	Ph_3SnH, xylene[c]
4. R = CN, 90%	R = H, 28%	Ph_3SnH, xylene[d]
		
5. R' = Me, 84%	R' = Me, 63%	Ph_3SnH, xylene[d]
6. R' = OMe, 96%	R' = OMe, 52%	Ph_3SnH, xylene[d]
7. R' = CO_2Me, 67%	R' = CO_2Me, 54%	Bu_3SnH, toluene[d]
		
8. R" = H, 94%	R" = H, 44%	Ph_3SnH, xylene[e]
9. R" = Me, 67%	R' = Me, 17%	Ph_3SnH, xylene[e]
		
10. 76%	41%	Bu_3SnH, xylene[d]
		
11. R = H, 92%	R = H, 8%	Ph_3SnH, toluene[d]
12. R = Me, 94%	R = Me, 25%	Ph_3SnH, benzene[d]

(continued)

Table 1 (continued)

		
13. R' = H, 80%	R' = H, 70%	Ph_3SnH, xylene[d]
14. R' = OMe, 63%	R' = OMe, 68%	Ph_3SnH, xylene[d]
		
15. R = H, Ar = Ph, 91%	R = H, Ar = Ph, 27%	Bu_3SnH, toluene[d]
16. R = CH_3, Ar = Ph, 79%[f]	R = CH_3, Ar = Ph, 73%	Bu_3SnH, toluene[d]
17. R = CH_3, Ar = 2-Naphthyl, 57%[f]	R = CH_3, Ar = 2-Naphthyl, 70%	Ph_3SnH, xylene[d]

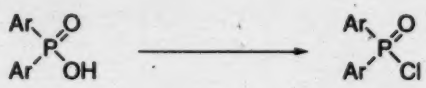
Legend for Table 1

[a]AIBN used as initiator in all cases. [b]Yield from the parent alcohol. [c]Workup with K_2CO_3, MeOH. [d]Workup with aqueous KF. [e]Workup with $NaCNBH_3$, *t*-BuOH. [f]Two diastereoisomers.

Experimental section

General Procedures. Unless stated to the contrary, the general experimental procedures used previously[43] were followed. The symbols s', d', t', and q' used for ^{13}C NMR signals indicate zero, one, two, or three attached hydrogens, respectively. ^{31}P NMR chemical shifts are referenced to external H_3PO_4 (1% in D_2O). In some of the ^{31}P spectra coupling constants are assigned for certain signals, but in most cases the components of spin-spin splitting multiplets were treated as individual signals.

General Procedure for the Preparation of Diarylphosphinic Chlorides.



An excess of $SOCl_2$ (2-3 mL) was added to the diarylphosphinic acid [$Ar_2P(O)OH$] (ca 300 mg), and the mixture was refluxed for 2 h, and then cooled. The excess of $SOCl_2$ was distilled off under water-pump vacuum (protection from moisture, oil bath taken up to 80 °C) and the residual diarylphosphinic chloride [$Ar_2P(O)Cl$] was used without purification.

General Procedure for Phosphinylation of Alcohols with Diarylphosphinic Chlorides.

The crude diarylphosphinic chloride, usually in a little CH_2Cl_2, was added over ca 10 min to a stirred solution of the alcohol, Et_3N, and DMAP in freshly distilled CH_2Cl_2. Stirring was continued until all the starting alcohol had been consumed (ca 1 h, TLC control, silica gel, EtOAc-hexane). Evaporation of the solvent, and flash chromatography of the residue over silica gel, using EtOAc-hexane, gave the required phosphinate.

2-(Bromophenyl)methyl Diphenylphosphinate (43.2a).

43.2a

The general procedure for phosphinylation was followed, using neat $Ph_2P(O)Cl$[44] (0.237 g, 0.19 mL, 1.0 mmol), (2-bromophenyl)methanol[44] (0.187 g, 1.0 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **43.2a** (0.329 g, 85%) as a white solid: mp 65-66 °C; FTIR (CH_2Cl_2

cast) 3057, 1439, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.14 (d, J = 7.0 Hz, 2 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.36-7.57 (m, 8 H), 7.75-7.95 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 65.7 (d, J = 4.0 Hz, t'), 122.7 (s'), 127.6, (d'), 128.6 (d'), 128.7 (d'), 129.5 (d'), 129.7 (d'), 131.2 (d, J = 136.0 Hz, s'), 131.7 (d'), 131.8 (d'), 132.4 (d'), 132.7 (d'), 135.8 (d, J = 7.7 Hz, s'); exact mass m/z calcd for $C_{19}H_{16}{}^{79}BrO_2P$ 386.0071, found 386.0033.

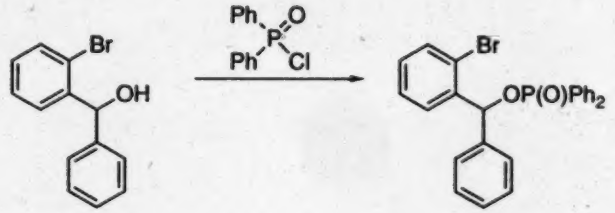
1-(2-Bromophenyl)ethyl Diphenylphosphinate (43.2b).

43.2b

The general procedure for phosphinylation was followed, using neat $Ph_2P(O)Cl$[44] (0.237 g, 0.19 mL), 2-bromo-α-methylbenzenemethanol[45] (0.201 g, 1.0 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **43.2b** (0.353 g, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3058, 2981, 1439, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.62 (d, J = 6.5 Hz, 3 H), 5.82 (dq, J = 9.5, 6.5 Hz, 1 H), 7.07 (dt, J = 7.5, 2.0 Hz, 1 H), 7.22-7.52 (m, 8 H), 7.60-7.70 (m, 3 H), 7.80-7.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.4 (q'), 73.5 (d, J = 4.3 Hz, d'), 121.0 (s'), 127.4 (d'), 127.8 (d'),

128.3 (d'), 128.4 (d'), 128.6 (d'), 129.1 (d'), 131.5 (d'), 131.6 (d, J = 235.1 Hz, s'), 131.6 (d'), 131.8 (d'), 131.9 (d'), 132.1 (d'), 132.2 (d'), 132.6 (d'), 141.8 (d, J = 5.1 Hz, s'); exact mass m/z calcd for $C_{20}H_{18}O_2P$ (M - Br) 321.1044, found 321.1045.

(2-Bromophenyl)phenylmethyl Diphenylphosphinate (43.2c).

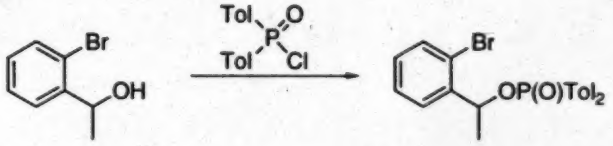


43.2c

The general procedure for phosphinylation was followed, using neat $Ph_2P(O)Cl$[44] (0.237 g, 0.19 mL, 1.0 mmol), 2-bromo-α-phenylbenzenemethanol[46] (0.263 g, 1.0 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:1 EtOAc-hexane, gave **43.2c** (0.273 g, 59%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3059, 1439, 1231 cm^{-1}; ^1H NMR (CD_2Cl_2, 600 MHz), 6.78 (d, J = 10.0 Hz, 1 H), 7.16 (dt, J = 7.5, 2.0 Hz, 1 H), 7.24-7.31 (m, 3 H), 7.35-7.55 (m, 10 H), 7.68-7.73 (m, 2 H), 7.75-7.81 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 77.2 (d, J = 10.2 Hz, d'), 122.3 (s'), 127.8 (d'), 128.1 (d'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 128.9 (d'), 129.0 (d'), 129.2 (d'), 129.8 (d'),

130.5 (s'), 130.7 (s'), 131.87 (d'), 131.92 (d'), 132.09 (d'), 132.12 (d'), 132.45 (d'), 132.51 (d'), 132.56 (d'), 133.1 (d'), 139.9 (s'), 140.0 (s'), 140.4 (s'), 140.5 (s'); exact mass *m/z* calcd for $C_{25}H_{20}{}^{79}BrO_2P$ 462.0384, found 462.0386.

1-(2-Bromophenyl)ethyl Bis(4-methylphenyl)phosphinate (45.3).

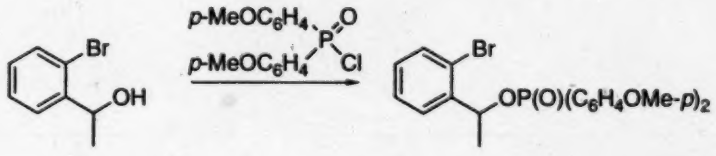


45.3

The general procedure for making phosphinic chlorides was followed, using bis(4-methylphenyl)phosphinic acid[11] (0.246 g, 1.0 mmol) and $SOCl_2$ (2 mL). The general procedure for phosphinylation was then followed, using the resulting bis(4-methylphenyl)phosphinic chloride, 2-bromo-α-methylbenzenemethanol[45] (0.201 g, 1.0 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **45.3** (0.360 g, 84%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 3022, 2980, 2923, 2866, 1603, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.62 (d, *J* = 6.5 Hz, 3 H), 2.36 (d, *J* = 23.2 Hz, 6 H), 5.79 (dq, *J* = 9.4, 6.5 Hz, 1 H), 7.09-7.16 (m, 3 H), 7.24-7.29 (m, 2 H), 7.35 (dt, *J* = 7.2, 1.5 Hz, 1 H), 7.44 (dd, *J* = 7.8, 1.5 Hz, 1

H), 7.51-7.58 (m, 2 H), 7.66 (dd, J = 8.0, 2.0 Hz, 1 H), 7.71-7.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.6 (d, J = 4.8 Hz, q'), 24.4 (q'), 73.3 (d, J = 4.9 Hz, d'), 121.0 (s'), 127.4 (d'), 127.5 (s'), 127.8 (d'), 128.5 (s'), 128.8 (s'), 129.01 (d'), 129.03 (d'), 129.1 (d'), 129.2 (d'), 129.3 (d'), 129.9 (s'), 131.5 (d'), 131.6 (d'), 131.8 (d'), 131.9 (d'), 132.6 (d'), 142.05 (s'), 142.10 (s'), 142.45 (s'), 142.49 (s'), 142.53 (s'); exact mass m/z calcd for $C_{22}H_{22}O_2P$ (M - Br) 349.1357, found 349.1356.

1-(2-Bromophenyl)ethyl Bis(4-methoxyphenyl)phosphinate (46.2).

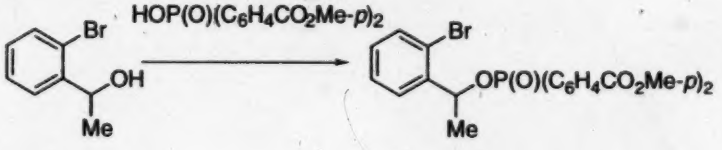


46.2

The general procedure for making phosphinic chlorides was followed, using bis(4-methoxyphenyl)phosphinic acid[44] (0.278 g, 1.0 mmol) and $SOCl_2$ (2 mL). The general procedure for phosphinylation was then followed, using the resulting bis(4-methoxyphenyl)phosphinic chloride, 2-bromo-α-methylbenzenemethanol[45] (0.201 g, 1.0 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 3:2 EtOAc-hexane, gave **46.2** (0.443 g, 96%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 3066, 2977,

2932, 2838, 1598, 1570, 1503, 1255, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (d, *J* = 6.5 Hz, 3 H), 3.68 (d, *J* = 14.5 Hz, 6 H), 5.72 (dq, *J* = 9.5, 6.5 Hz, 1 H), 6.74 (dd, *J* = 8.5, 2.5 Hz, 2 H), 6.87 (dd, *J* = 8.5, 2.5 Hz, 2 H), 7.00 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.25 (dt, *J* = 7.5, 1.0 Hz, 1 H), 7.33 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.52 (dd, *J* = 11.5, 8.5 Hz, 2 H), 7.58 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.72 (dd, *J* = 11.5, 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.3 (d, *J* = 3.5 Hz, q'), 55.22 (q'), 55.25 (q'), 73.0 (d, *J* = 6.5 Hz, d'), 113.8 (d'), 113.9 (d'), 114.0 (d'), 114.1 (d'), 120.9 (s'), 121.9 (s'), 122.8 (s'), 123.7 (s'), 124.8 (s'), 127.4 (d'), 127.8 (d'), 129.0 (d'), 132.5 (d'), 133.2 (d'), 133.4 (d'), 133.5 (d'), 133.6 (d'), 141.98 (s'), 142.04 (s'), 162.44 (s'), 162.49 (s'), 162.54 (s'); exact mass *m/z* calcd for $C_{22}H_{22}O_4P$ (M - Br) 381.1256, found 381.1250.

4,4'-[[1-(2-Bromophenyl)ethoxy]phosphinylidene]-bisbenzoic Acid Dimethyl Ester (47.3).

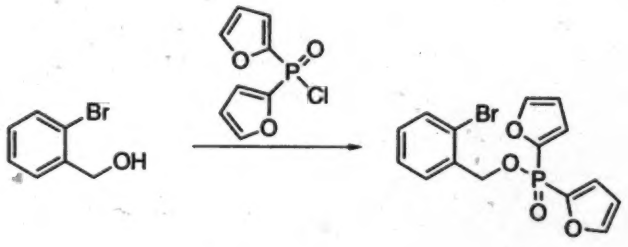


47.3

The general procedure for making phosphinic chlorides was followed, using 4,4'-phosphinicobisbenzoic acid dimethyl ester[12] [$(p\text{-}MeO_2CC_6H_4)_2P(O)OH$] (0.651 g, 1.95 mmol) and $SOCl_2$ (2 mL). The general procedure for phosphinylation was then

followed, using the resulting phosphinic chloride, 2-bromo-α-methylbenzenemethanol[45] (0.382 g, 1.90 mmol), Et_3N (1 mL) and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **47.3** (0.658 g, 67%) as a white solid: mp 115-116 °C; FTIR (CH_2Cl_2 cast) 2984, 2951, 1727, 1435, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, *J* = 6.5 Hz, 3 H), 3.91 (d, *J* = 8.2 Hz, 6 H), 5.86 (dq, *J* = 9.2, 6.5 Hz, 1 H), 7.10 (dt, *J* = 7.8, 1.8 Hz, 1 H), 7.34 (dt, *J* = 7.8, 1.5 Hz, 1 H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.61 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.67-7.76 (m, 2 H), 7.87-8.00 (m, 4 H), 8.08-8.15 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.2 (d, *J* = 2.8 Hz, q'), 52.41 (q'), 52.46 (q'), 74.3 (d, *J* = 6.5 Hz, d'), 121.1 (s'), 127.3 (d'), 127.9 (d'), 129.3 (d'), 129.4 (d'), 129.5 (d'), 129.7 (d'), 131.5 (d'), 131.6 (d'), 131.8 (d'), 131.9 (d'), 132.8 (d'), 133.5 (s'), 133.60 (s'), 133.63 (s'), 134.6 (s'), 135.3 (s'), 136.3 (s'), 137.2 (s'), 141.0 (s'), 141.1 (s'), 166.1 (s'); exact mass *m/z* calcd for $C_{24}H_{22}O_6P$ (M - Br) 437.1154, found 437.1153.

(2-Bromophenyl)methyl Di-2-furanylphosphinate (48.4a).

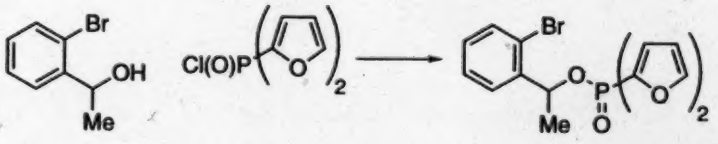


48.4a

The general procedure for making phosphinic chlorides was followed, using di-2-furanylphosphinic acid[14] (prepared by alkaline hydrolysis[14] of tri(2-furyl)phosphine oxide)[13] (0.387 g, 1.95 mmol) and $SOCl_2$ (2 mL). The general procedure for phosphinylation was then followed, using the resulting di-2-furanylphosphinic chloride, 2-bromobenzemethanol[44] (0.355 g, 1.90 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **48.4a** (0.655 g, 94%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 3127, 2954, 1555, 1460, 1251 cm^{-1}; ^1H NMR (300 MHz) δ 5.12 (d, J = 8.0 Hz, 2 H), 6.37-6.42 (m, 2 H), 7.06 (dt, J = 7.2, 1.7 Hz, 1 H) 7.14-7.27 (m, 3 H), 7.42 (t, J = 7.5 Hz, 2 H), 7.54-7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 66.4 (d, J = 9.2 Hz, t'), 110.7 (d, J = 19.7 Hz, d'), 122.2 (s'), 123.2 (d, J = 47.4 Hz, d'), 127.4 (d'), 129.1 (d'), 129.6 (d'), 132.4 (d'), 134.9 (d, J = 15.5 Hz, s'), 145.1 (d, J = 391.8 Hz, s'), 148.5 (d, J = 19.9 Hz, d'); exact mass m/z calcd for $C_{15}H_{12}O_4P$ [M - Br] 287.0473, found

287.0471.

1-(2-Bromophenyl)ethyl Di-2-furanylphosphinate (48.4b).

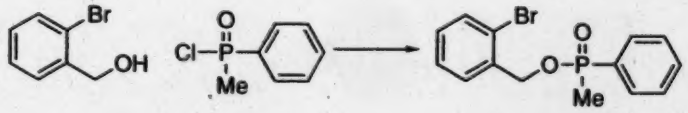


48.4b

The general procedure for making phosphinic chlorides was followed, using di-2-furanylphosphinic acid[14] (0.387 g, 1.95 mmol) and $SOCl_2$ (2 mL). The general procedure for phosphinylation was then followed, using the resulting di-2-furanylphosphinic chloride, 2-bromo-α-methylbenzenemethanol[45] (0.382 g, 1.90 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **48.4b** (0.487 g, 67%) as a light yellow oil: FTIR (CH_2Cl_2 cast) 3115, 2982, 2931, 1460, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61 (d, J = 6.5 Hz, 3 H), 5.86 (dq, J = 10.5, 6.5 Hz, 1 H), 6.36-6.40 (m, 1 H), 6.46-6.50 (m, 1 H), 7.05-7.13 (m, 2 H), 7.20-7.23 (m, 1 H), 7.32 (dt, J = 7.5, 1.2 Hz, 1 H), 7.42 (dd, J = 8.0, 1.2 Hz, 1 H), 7.47-7.50 (m, 1 H), 7.62 (dd, J = 7.5, 1.8 Hz, 1 H), 7.65-7.68 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.1 (d, J = 5.3 Hz, q'), 74.4 (d, J = 6.4 Hz, d'), 110.6 (d'), 110.74 (d'), 110.77 (d'), 110.9 (d'), 120.6 (s'), 122.7 (d'), 123.02 (d'), 123.09 (d'), 123.40 (d'), 127.3 (d'), 127.8 (d'), 129.1 (d'),

132.4 (d'), 141.1 (d, J = 6.5 Hz, s'), 145.4 (d, J = 255.6 Hz, s'), 146.0 (d, J = 265.1 Hz, s'), 148.3 (d, J = 13.1 Hz, d'); exact mass m/z calcd for $C_{16}H_{14}O_4P$ [M - Br] 301.0630, found 301.0630.

(2-Bromophenyl)methyl Methylphenylphosphinate (53.4a).

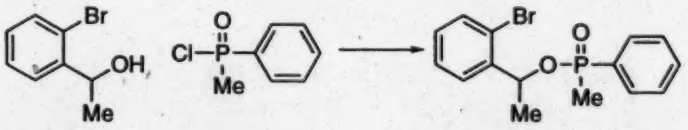


43.1a **53.3** **53.4a**

The procedure for phosphinylation was followed, using 2-bromobenzemethanol[44] (0.187 g, 1.0 mmol), methylphenylphosphinic chloride[22] (**53.3**) (0.209 g, 1.2 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 2:1 EtOAc-hexane, gave **53.4a** (0.296 g, 91%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3058, 2988, 2916, 1439, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72 (d, J = 14.5 Hz, 3 H), 4.97 [AB q, J_{AB} = 12.5 Hz, Δ_{AB} = 80.8 Hz, 2 H, each signal of the AB q is split into a d (J = 6.8 Hz) by coupling to ^{31}P], 7.11 (dt, J = 7.5, 1.8 Hz, 1 H), 7.26 (dt, J = 7.5, 1.2 Hz, 1 H), 7.39-7.56 (m, 5 H), 7.74-7.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.9 (d, J = 101.5 Hz, q'), 65.3 (d, J = 5.1 Hz, t'), 122.6 (s'), 127.4 (d'), 128.5 (d'), 128.6 (d'), 129.3 (d'), 129.5 (d'), 131.0 (d'), 131.2 (d, J = 127.1 Hz, s'), 131.2 (d'), 132.29

(d'), 132.32 (d'), 132.5 (d'), 135.7 (d, J = 7.5 Hz, s'); exact mass m/z calcd for $C_{14}H_{14}{}^{79}BrO_2P$ 323.9915, found $C_{14}H_{14}{}^{79}BrO_2P$ 323.9897.

1-(2-Bromophenyl)ethyl Methylphenylphosphinate (53.4b).



43.1b **53.3** **53.4b**

The general procedure for phosphinylation was followed, using 2-bromo-α-methylbenzenemethanol[44,45] (0.201 g, 1.0 mmol), methylphenylphosphinic chloride[22] (**53.3**) (0.209 g, 1.2 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 2:1 EtOAc-hexane, gave a mixture of the two diastereoisomers of **53.4b** (0.268 g in all, 79%) as a colorless oil. Small samples of the individual isomers were obtained by flash chromatography, using the above system. The less polar isomer of **53.4b** had: FTIR (CH_2Cl_2 cast) 3058, 2981, 2929, 1438, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, J = 6.5 Hz, 3 H), 1.59 (d, J = 14.5 Hz, 3 H), 5.82 (dq, J = 9.5, 6.5 Hz, 1 H), 7.13 (dt, J = 7.8, 1.8 Hz, 1 H), 7.35 (dt, J = 7.5, 0.5 Hz, 1 H), 7.44-7.63 (m, 5 H), 7.79-7.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.0 (d, J = 98.6 Hz, q'), 23.93 (q'), 23.98 (q'), 72.7 (d, J = 5.7 Hz, d'), 121.0 (s'), 127.2 (d'),

127.9 (d'), 128.5 (d'), 128.6 (d'), 129.2 (d'), 130.8 (d'), 131.0 (d'), 132.23 (d'), 132.25 (d'), 132.6 (d, J = 131.0 Hz, s'), 132.8 (d'), 142.0 (s'); exact mass m/z calcd for $C_{15}H_{16}O_2P$ [M - Br] 259.0888, found 259.0887.

The more polar isomer of **53.4b** had: FTIR (CH_2Cl_2 cast) 3058, 2982, 2928, 1439, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (d, J = 6.5 Hz, 3 H), 1.72 (d, J = 14.6 Hz, 3 H), 5.60 (dq, J = 10.2, 6.5 Hz, 1 H), 7.06 (dt, J = 7.8, 2.0 Hz, 1 H), 7.24-7.36 (m, 4 H), 7.39-7.47 (m, 1 H), 7.50-7.63 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.1 (d, J = 103.3 Hz, q'), 24.5 (q'), 73.0 (d, J = 5.1 Hz, d'), 121.0 (s'), 127.4 (d'), 127.6 (d'), 128.2 (d'), 128.4 (d'), 129.0 (d'), 130.4 (s'), 131.2 (d'), 131.3 (d'), 132.08 (d'), 132.11 (d'), 132.4 (d'), 141.67 (s'), 141.74 (s'); ; exact mass m/z calcd for $C_{15}H_{16}O_2P$ [M - Br] 259.0888, found 259.0893.

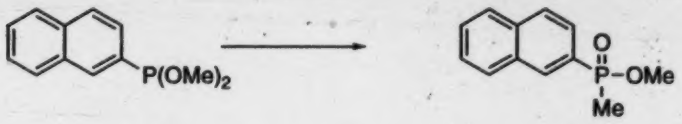
1-(2-Bromophenyl)ethyl Methyl-2-naphthalenylphosphinate (54.6).

(a) Dimethyl 2-naphthalenylphosphonite.

Methyl methyl-2-naphthalenephosphinate [2-$C_{10}H_7P(O)(Me)OMe$] was made by preparing first 2-naphthalenylphosphonous dichloride[24] [2-$C_{10}H_7PCl_2$] and then following a procedure reported[22] for the corresponding phenylphosphinate.

2-Bromonaphthalene (4.858 g, 23.5 mmol) in Et_2O (10 mL) was added dropwise to a stirred suspension of Mg (0.676 g, 27.8 mmol) in Et_2O (30 mL) to which a crystal of I_2 had been added. After ca 4 mL had been added, the mixture began to reflux gently, and the rate of addition was controlled to maintain gentle reflux. At the end of the addition, refluxing was continued for 4 h, and the mixture was then cooled to room temperature and added over 1.5 h to a stirred and cooled (-78 °C) solution of chlorobis(diethylamino)-phosphine[24] (4.938 g, 23.5 mmol) in Et_2O (50 mL). The mixture was stirred overnight, the ice bath being left in place, but not recharged. The mixture was then refluxed for 30 min, cooled (ice bath) and stirred while HCl was bubbled into it for ca 1 h. The cold bath was removed, and the mixture was stirred for 2 h, and then filtered. The filtrate was concentrated (rotary evaporator, water-pump, protection from moisture) and distilled under reduced pressure (110 °C/0.2 mmHg) to give 2-$C_{10}H_7PCl(NEt_2)$ as a yellow oil. A mixture of dry MeOH (25 mL) and hexane (10 mL) was added slowly (ca 2 h) under N_2 to a stirred and cooled (0 °C) solution of the oil in hexane (30 mL) (N_2 atmosphere). Stirring was continued for 1 h, at which stage the ice bath was removed. When the mixture had attained room temperature, it was evaporated on a rotary evaporator (protection from moisture), and the residual dimethyl 2-naphthalenyl-phosphonite [2-$C_{10}H_7P(OMe)_2$] was used in the next step without further purification.

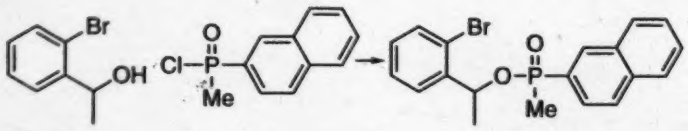
(b) Methyl Methyl-2-naphthalenylphosphinate.



55.4

The crude phosphonite was added to stirred MeI (3 mL) under N_2 at room temperature, and the mixture was refluxed overnight. The mixture was cooled, and flash chromatography over silica gel (3.5 x 25 cm), using 10:1 EtOAc-hexane, gave methyl methyl-2-naphthalenylphosphinate as a colorless oil (1.057, 20% overall from 2-bromonaphthalene): FTIR (CH_2Cl_2 cast) 3453, 3054, 2986, 2946, 2917, 2843 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.72 (d, J = 14.8 Hz, 3 H), 3.62 (d, J = 11.5 Hz, 3 H), 7.57 (ddq, J = 7.5, 7.5, 2.0 Hz, 2 H), 7.65-7.72 (m, 1 H), 7.84-7.89 (m, 1 H), 7.89-7.96 (m, 2 H), 8.42 (d, J = 14.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.3 (d, J = 103.5 Hz, q'), 50.8 (d, J = 6.3 Hz, q'), 125.5 (d'), 125.7 (d'), 126.79 (d'), 126.81 (d'), 126.82 (d'), 127.62 (d'), 127.64 (d'), 127.65 (d'), 127.9 (d, J = 126.7 Hz, s'), 128.1 (d'), 128.4 (d'), 128.5 (d'), 128.72 (d'), 132.3 (d, J = 13.8 Hz, s'), 133.5 (d'), 133.6 (d'), 134.8 (d, J = 2.4 Hz, s'); exact mass m/z for $C_{12}H_{13}O_2P$ 220.0653, found 220.0652.

(c) 1-(2-Bromophenyl)ethyl Methyl-2-naphthalenylphosphinate (54.6).



43.1b **54.5** **54.6**

Methyl-2-naphthalenylphosphinic chloride [2-$C_{10}H_7P(O)(Me)Cl$] was made from methyl methyl-2-naphthalenylphosphinate (0.364 g, 1.65 mmol) by treatment with PCl_5, according to a procedure reported[22] for the corresponding phenylphosphinate, and the compound was used directly, without characterization.

The general procedure for phosphinylation was followed, using the above methyl-2-naphthalenylphosphinic chloride, 2-bromo-α-methylbenzenemethanol[44,45] (0.362 g, 1.80 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in dry CH_2Cl_2 (20 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:1 EtOAc-hexane, gave a mixture of the two diastereoisomers of **54.6** (0.365 g in all, 57%) as a colorless liquid. Small amounts of the individual isomers were obtained by flash chromatography. The less polar isomer of **54.6** had: FTIR (CH_2Cl_2 cast) 3055, 2981, 2929, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.46 (d, J = 6.5 Hz, 3 H), 1.69 (d, J = 14.5 Hz, 3 H), 5.87 (dq, J = 10.0, 6.5 Hz, 1 H), 7.08-7.18 (m, 1 H), 7.32-7.42 (m, 1 H), 7.46-7.68 (m, 4 H), 7.72-8.00 (m, 4 H), 8.48 (d, J = 13.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.1 (d, J = 98.9 Hz, q'),

23.95 (q'), 24.00 (q'), 72.8 (d, J = 5.7 Hz, d'), 121.0 (s'), 125.6 (d'), 125.7 (d'), 127.0 (d'), 127.2 (d'), 127.86 (d'), 127.89 (d'), 128.3 (d'), 128.4 (d'), 128.6 (d'), 128.7 (s'), 129.0 (d'), 129.2 (d'), 130.4 (s'), 132.4 (s'), 132.6 (s'), 132.8 (d'), 133.2 (d'), 133.3 (d'), 134.9 (s'), 142.0 (s'), 142.1 (s'); exact mass m/z calcd for $C_{19}H_{18}{}^{79}BrO_2P$ 388.0228, found 388.0223.

The more polar isomer of **54.6** had: FTIR (CH_2Cl_2 cast) 3055, 2981, 2928, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.63 (d, J = 6.2 Hz, 3 H), 1.79 (d, J = 14.5 Hz, 3 H), 5.67 (dq, J = 10.0, 6.2 Hz, 1 H), 6.98-7.04 (m, 1 H), 7.28-7.31 (m, 2 H), 7.38-7.59 (m, 4 H), 7.68-7.84 (m, 3 H), 8.28 (d, J = 13.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.2 (d, J = 102.9 Hz, q'), 24.43 (q'), 24.46 (q'), 73.1 (d, J = 5.4 Hz, d'), 121.0 (s'), 125.6 (d'), 125.8 (d'), 126.8 (d'), 127.5 (d'), 127.65 (d'), 127.71 (d'), 128.1 (d'), 128.3 (d'), 128.9 (d'), 129.0 (d'), 129.1 (s'), 132.3 (s'), 132.4 (d'), 133.7 (d'), 133.8 (d'), 141.6 (s'), 141.7 (s'); exact mass m/z calcd for $C_{19}H_{18}{}^{79}BrO_2P$ 388.0228, found 388.0225.

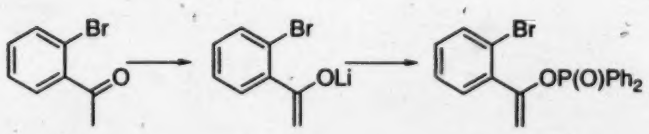
(2-Bromophenyl)cyanomethyl Diphenylphosphinate (57.2).

57.1 **57.2**

The general procedure for phosphinylation was followed,

using neat $Ph_2P(O)Cl$[44] (0.180 g, 0.15 mL, 0.76 mmol), α-hydroxy(2-bromobenzene)acetonitrile[50] (0.161 g, 0.76 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:2 EtOAc-hexane, gave **57.2** (0.283 g, 90%) as a thick, yellow oil: FTIR (CH_2Cl_2 cast) 3059, 1959, 1439, 1232 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 6.46 (d, J = 10.0 Hz, 1 H), 7.25 (dt, J = 7.8, 1.8 Hz, 1 H), 7.33-7.44 (m, 3 H), 7.47-7.56 (m, 4 H), 7.56-7.64 (m, 1 H), 7.67-7.77 (m, 3 H), 7.86-7.95 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 63.3 (d, J = 4.7 Hz, d'), 115.7 (d, J = 4.4 Hz, s'), 122.3 (s'), 128.3 (d'), 128.6 (d'), 128.8 (d'), 128.9 (d'), 129.1 (s'), 129.4 (d'), 130.5 (s'), 130.9 (s'), 131.5 (d'), 131.6 (d'), 131.76 (d'), 131.79 (d'), 131.9 (d'), 132.42 (s'), 132.48 (s'), 132.89 (d'), 132.92 (d'), 133.15 (d'), 133.19 (d'), 133.5 (d'); exact mass m/z calcd for $C_{20}H_{15}NO_2P$ (M - Br) 332.0841, found 332.0842.

1-(2-Bromophenyl)ethenyl Diphenylphosphinate (58.3).

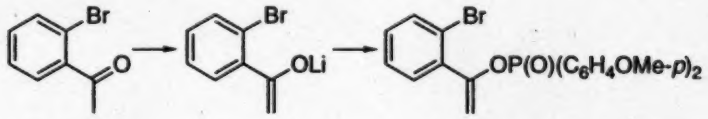


58.1 **58.3**

A solution of LDA was prepared by dropwise addition of *n*-BuLi (2.5 M in hexane, 1.44 mL) to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.364 g, 0.50 mL, 3.60 mmol) in THF

(10 mL). Stirring at 0 °C was continued for 20 min, and a solution of 1-(2-bromophenyl)ethanone[51] (0.597 g, 3.00 mmol) [made from 2-bromo-α-methylbenzenemethanol[44,45] by PCC oxidation] in THF (20 mL) was added dropwise. Stirring at 0 °C was continued for 1 h, and neat $Ph_2P(O)Cl$[44] (0.851 g, 0.69 mL, 3.6 mmol) was then injected. Stirring was continued for 30 min at 0 °C, and the mixture was then quenched with water at 0 °C, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 1:1 EtOAc-hexane, gave **58.3** (0.958 g, 80%) as a colorless liquid: FTIR (CH_2Cl_2 cast) 3057, 1646, 1439, 1290, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 4.87-4.92 (m, 1 H), 5.35-5.40 (m, 1 H), 7.09-7.27 (m, 3 H), 7.34-7.43 (m, 4 H), 7.44-7.55 (m, 3 H), 7.78-7.88 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 104.2 (d, J = 5.3 Hz, t'), 121.8 (s'), 127.1 (d'), 128.3 (d'), 128.5 (d'), 130.1 (s'), 130.2 (d'), 131.0 (d, J = 139.0 Hz, s'), 131.0 (d'), 131.7 (d'), 131.8 (d'), 132.0 (s'), 132.3 (d'), 133.1 (d'), 137.16 (s'), 137.23 (s'), 151.7 (d, J = 9.1 Hz, s'); exact mass m/z calcd for $C_{20}H_{16}{}^{79}BrO_2P$ 398.0071, found 398.0069.

1-(2-Bromophenyl)ethenyl Bis(4-methoxyphenyl)-phosphinate (59.2).

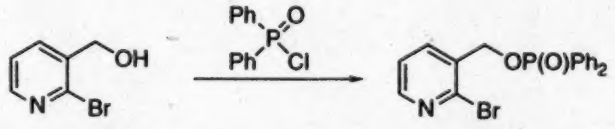


58.1 **59.2**

A solution of LDA was prepared by dropwise addition of *n*-BuLi (2.5 M in hexane, 0.66 mL) to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.167 g, 0.23 mL, 1.65 mmol) in THF. Stirring at 0 °C was continued for 10 min, and then 1-(2-bromophenyl)ethanone[51] (0.272 g, 1.37 mmol) [made from 2-bromo-α-methylbenzenemethanol[44,45] by PCC oxidation] in THF (10 mL) was added. Stirring was continued at 0 °C for 1 h. Bis(4-methoxyphenyl)phosphinic chloride [made from bis(4-methoxyphenyl)phosphinic acid[44] (0.419 g, 1.51 mmol) and $SOCl_2$ (3 mL), as described above (see preparation of **46.2**)] in THF (5 mL), was then injected dropwise, and stirring was continued for 30 min at 0 °C. The mixture was quenched with water at 0 °C, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:1 EtOAc-hexane, gave **59.2** (0.395 g, 63%) as a light brown oil: FTIR (CH_2Cl_2 cast) 1645, 1598, 1503 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 3.80 (s, 6 H), 4.87 (t, *J* = 2.2 Hz, 1 H), 5.32-5.36 (m, 1 H), 6.85-6.92 (m, 4 H), 7.09-7.25 (m, 3 H), 7.52 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.69-7.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 55.3 (q'), 103.8 (d, *J* = 5.3 Hz, t'),

113.8 (d'), 114.0 (d'), 122.8 (d, J = 146.1 Hz, s'), 127.1 (d'), 130.0 (d'), 131.1 (d'), 133.1 (d'), 133.6 (d'), 133.7 (d'), 137.47 (s'), 137.53 (s'), 151.7 (d, J = 9.5 Hz, s'), 162.6 (s'); exact mass m/z calcd for $C_{22}H_{20}{}^{79}BrO_4P$ 458.0283, found 458.0287.

(2-Bromo-3-pyridinyl)methyl Diphenylphosphinate (61.1).



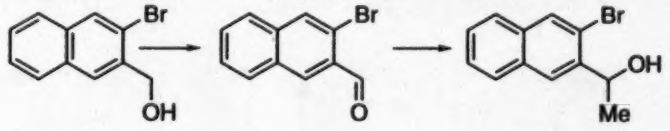
61.1

The general procedure for phosphinylation was followed, using neat $Ph_2P(O)Cl$[44] (0.237 g, 1.0 mmol, 0.19 mL), 2-bromo-3-pyridinemethanol[48,49] (0.188 g, 1.0 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 2:1 EtOAc-hexane, gave **61.1** (0.295 g, 76%) as a white solid: mp 101-102 °C; FTIR (CH_2Cl_2 cast) 3055, 1410, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), 5.11 (d, J = 7.5 Hz, 2 H), 7.27 (dd, J = 7.0, 4.8 Hz, 1 H), 7.44-7.50 (m, 4 H), 7.52-7.58 (m, 2 H), 7.81-7.89 (m, 5 H), 8.29 (dd, J = 4.8, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 64.4 (d, J = 3.6 Hz, t'), 123.0 (d'), 128.68 (d'), 128.75 (d'), 128.77 (d'), 128.81 (d'), 130.7 (d, J = 135.8 Hz, s'), 131.58 (d'), 131.62 (d'), 131.64 (d'), 131.68 (d'), 132.56 (d'), 132.59 (d'), 133.5 (s'), 133.6 (s'), 137.4 (d'), 141.8 (s'), 149.4

(d'); exact mass *m/z* calcd for $C_{18}H_{15}{}^{79}BrNO_2P$ 387.0024, found 387.0025.

1-(3-Bromo-2-naphthalenyl)ethyl Diphenylphosphinate (67.3).

(a) α-Methyl(3-bromo-2-naphthalene)methanol.



65.5 **67.1** **67.2**

PCC (0.162 g, 0.75 mmol) was added to a stirred solution of 3-bromo-2-naphthalenemethanol[26b] [made from the bis(hexachlorocyclopentadiene) adduct of 2-methylnaphthalene[26b,29]] (0.119 g, 0.50 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 2 h, and the mixture was filtered. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:10 EtOAc-hexane, gave 3-bromo-2-naphthaldehyde[47] as a white solid (0.113 g, 96%), which was used directly in the next step.

MeMgBr (3.0 M in Et_2O, 0.20 mL) was injected over ca 10 min into a stirred and cooled (0 °C) solution of 3-bromo-2-naphthaldehyde (0.113 g, 0.48 mmol) in dry Et_2O (10 mL). The ice bath was left in place, but not recharged, and stirring was continued for 1 h. The mixture was then quenched at 0 °C with hydrochloric acid (2 M, 10 mL) and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash

chromatography of the residue over silica gel (2.5 x 20 cm), using 1:4 EtOAc-hexane, gave α-methyl(3-bromo-2-naphthalene)methanol (0.117 g, 97%) as a white solid: mp 86-87 °C; FTIR (CH_2Cl_2 cast) 3600-3100, 3054, 2972, 2927 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.59 (d, J = 6.5 Hz, 3 H), 2.11 (s, 1 H), 5.35 (q, J = 6.5 Hz, 1 H), 7.44-7.53 (m, 2 H), 7.69-7.76 (m, 1 H), 7.79-7.86 (m, 1 H), 8.05 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.0 (q'), 69.3 (d'), 119.9 (s'), 125.5 (d'), 126.5 (d'), 126.6 (d'), 126.7 (d'), 128.0 (d'), 131.4 (d'), 132.5 (s'), 133.6 (s'), 142.0 (s'); exact mass m/z calcd for $C_{12}H_{11}{}^{79}BrO$ 249.9993, found 249.9987.

(b) 1-(3-Bromo-2-naphthalenyl)ethyl Diphenylphosphinate (67.3).

67.3

The general procedure for phosphinylation was followed, using neat $Ph_2P(O)Cl$[44] (0.129 g, 0.55 mmol, 0.10 mL), α-methyl(3-bromo-2-naphthalene)methanol (0.115 g, 0.46 mmol), Et_3N (1 mL), and DMAP (ca 6 mg, 0.05 mmol) in dry CH_2Cl_2 (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:1 EtOAc-hexane, gave **67.3** (0.195 g, 94%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3056, 2981, 2929, 1439, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.75 (d, J = 6.2 Hz, 3 H), 5.97 (dq, J = 9.5, 6.2 Hz, 1 H), 7.25-7.33 (m, 2 H), 7.37-7.44 (m, 1 H),

7.44-7.57 (m, 5 H), 7.67-7.76 (m, 3 H), 7.79-7.86 (m, 1 H), 7.88-7.96 (m, 2 H), 7.98 (s, 1 H), 8.09 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.9 (q'), 73.8 (d, J = 4.9 Hz, d'), 118.8 (s'), 126.57 (d'), 126.60 (d'), 126.62 (d'), 127.0 (d'), 128.0 (d'), 128.3 (d'), 128.5 (d'), 128.6 (d'), 130.4 (s'), 131.3 (s'), 131.4 (d'), 131.5 (d'), 131.6 (d'), 131.7 (d'), 131.9 (d'), 132.09 (d'), 132.11 (d'), 132.2 (d'), 132.3 (s'), 133.1 (s'), 133.7 (s'), 139.08 (s'), 139.15 (s'); exact mass m/z calcd for $C_{24}H_{20}O_2P$ (M - Br) 371.1201, found 371.1219.

General Procedure for Radical Aryl Transfer.

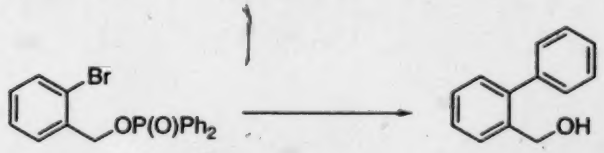
Departures from the usual procedure are specifically indicated in the appropriate experimental procedures.

The substrate (0.2-0.5 mmol) was placed in a 100-mL oven-dried round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser sealed with a rubber septum. The system was flushed with argon for 5-10 min, and dry xylene (20-40 mL) was injected. [In a few experiments PhH or PhMe were used.] The flask was lowered into an oil bath that had been preheated to 120°C (85 °C for PhH, 110 °C for PhMe), and a solution of Ph_3SnH (2 equiv., 0.03-0.06 M) and AIBN (0.5 equiv., 0.006-0.016 M) in xylene was injected over 10 h with a syringe pump. [In a few experiments, Bu_3SnH was used instead of Ph_3SnH.] Refluxing was continued for an arbitrary period of 2 h after the end of the addition, and the mixture was then cooled and evaporated. The residue was taken up in Et_2O (ca 20 mL) and stirred with saturated

aqueous KF (10 mL) for ca 30 min. The precipitated triphenyltin fluoride was removed by filtration, and the ether layer was dried ($MgSO_4$) and evaporated. The residue was then processed as described for the individual examples.

In several cases KF was not used; the original xylene solution was evaporated and the residue was stirred with K_2CO_3-MeOH. In two experiments, the original xylene solution was evaporated and the residue was dissolved in *t*-BuOH. $NaCNBH_3$ was added, and the mixture was refluxed for 1 h.

[1,1'-Biphenyl]-2-methanol (43.3a).



43.2a **43.3a**

The general procedure for radical aryl transfer was followed, using phosphinate **43.2a** (0.116 g, 0.30 mmol) in xylene (30 mL), and Ph_3SnH (0.210 g, 0.60 mmol) and AIBN (0.025 g, 0.15 mmol) in xylene (20 mL). The xylene was evaporated, the residue was covered with MeOH (50 mL), and K_2CO_3 (ca 0.2 g) was added. The mixture was stirred for 30 min, and then filtered. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **43.3a**[52] (0.032 g, 58%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3500-3100 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.55 (s, 1 H), 4.63 (s, 2 H), 7.23-7.64 (m, 9 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 63.2 (t'), 127.3 (d'),

127.70 (d'), 127.74 (d'), 128.3 (d'), 128.4 (d'), 129.1 (d'), 130.1 (d'), 138.1 (s'), 140.7 (s'), 141.4 (s'); exact mass *m/z* calcd for $C_{13}H_{12}O$ 184.0888, found 184.0894.

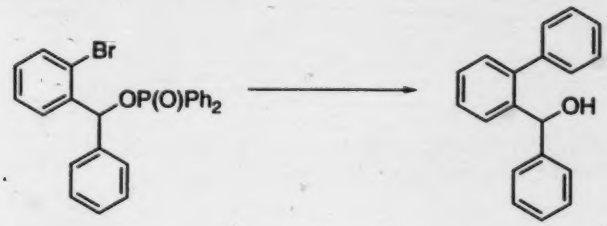
α-Methyl[1,1'-biphenyl]-2-methanol (43.3b).

43.2b **43.3b**

The general procedure for radical aryl transfer was followed, using phosphinate **43.2b** (0.140 g, 0.35 mmol) in xylene (30 mL), and Ph_3SnH (0.246 g, 0.70 mmol) and AIBN (0.029 g, 0.18 mmol) in xylene (20 mL). The xylene was evaporated, the residue was covered with MeOH (50 mL), and K_2CO_3 (ca 0.2 g) was added. The mixture was stirred for 30 min, and then filtered. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **43.3b**[53] (0.044 g, 64%) as a white solid: mp 109-110 °C (lit.[53] 111-112 °C); FTIR (CH_2Cl_2 cast) 3500-3150 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, *J* = 6.5 Hz, 3 H), 1.47 (s, 1 H), 4.99 (q, *J* = 6.5 Hz, 1 H), 7.22 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.28-7.46 (m, 7 H), 7.69 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, (100.6 MHz) δ 24.9 (q'), 66.5 (d'), 125.4 (d'), 127.16 (d'), 127.19 (d'), 128.1 (d'), 128.2 (d'), 129.3 (d'), 130.0 (d'), 140.4 (s'), 141.0 (s'), 143.1 (s'); exact mass *m/z* calcd for $C_{14}H_{14}O$ 198.1044, found

198.1049.

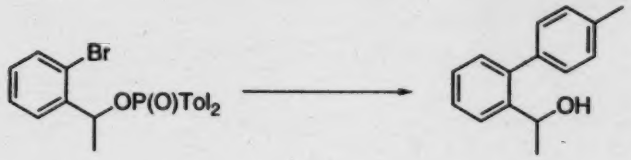
α-Phenyl[1,1'-biphenyl]-2-methanol (43.3c).



43.2c **43.3c**

The general procedure for radical aryl transfer was followed, using phosphinate **43.2c** (0.187 g, 0.40 mmol) in xylene (30 mL), and Ph_3SnH (0.281 g, 0.80 mmol) and AIBN (0.033 g, 0.20 mmol) in xylene (20 mL). The xylene was evaporated, the residue was covered with MeOH (50 mL), and K_2CO_3 (ca 0.2 g) was added. The mixture was stirred for 30 min, and then filtered. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **43.3c**[54] (0.048 g, 46%) as a white solid: mp 59-60 °C (lit. [54b] 66-68 °C); FTIR (CH_2Cl_2 cast) 3500-3100 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.20 (s, 1 H), 5.93 (s, 1 H), 7.13-7.42 (m, 13 H), 7.54 (dd, J = 7.5, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 72.5 (d'), 126.6 (d'), 127.2 (d'), 127.4 (d'), 127.9 (d'), 128.15 (d'), 128.22 (d'), 129.4 (d'), 130.0 (d'), 140.8 (s'), 141.1 (s'), 141.4 (s'), 143.9 (s'); exact mass m/z calcd for $C_{19}H_{16}O$ 260.1201, found 260.1204.

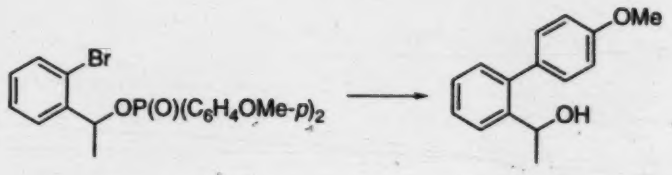
α,4'-Dimethyl[1,1'-biphenyl]-2-methanol (45.4).



45.3 **45.4**

The general procedure for radical aryl transfer was followed, using phosphinate **45.3** (0.183 g, 0.43 mmol) in xylene (30 mL), and Ph_3SnH (0.302 g, 0.86 mmol) and AIBN (0.035 g, 0.21 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **45.4**[55] (0.057 g, 63%) as a white solid: mp 83-84 °C (lit.[55] 84-85 °C); FTIR (CH_2Cl_2 cast) 3500-3200 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, J = 6.5 Hz, 3 H), 1.71 (s, 1 H), 2.42 (s, 3 H), 5.01 (q, J = 6.5 Hz, 1 H), 7.19-7.27 (m, 5 H), 7.31 (dt, J = 7.5, 1.5 Hz, 1 H), 7.41 (dt, J = 7.5, 1.5 Hz, 1 H), 7.77 (dd, J = 8.0, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.2 (q'), 24.9 (q'), 66.5 (d'), 125.4 (d'), 127.1 (d'), 127.9 (d'), 128.9 (d'), 129.2 (d'), 130.1 (d'), 136.8 (s'), 138.0 (s'), 140.4 (s'), 141.2 (s'); exact mass m/z calcd for $C_{15}H_{16}O$ 212.1201, found 212.1200.

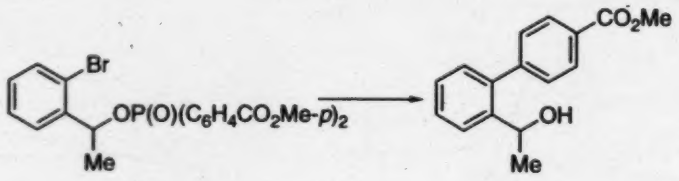
4'-Methoxy-α-methyl[1,1'-biphenyl]-2-methanol (46.3).



46.2 **46.3**

The general procedure for radical aryl transfer was followed, using phosphinate **46.2** (0.146 g, 0.32 mmol) in xylene (20 mL), and Ph_3SnH (0.225 g, 0.64 mmol) and AIBN (0.026 g, 0.16 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:8 EtOAc-hexane, gave **46.3** (0.038 g, 52%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3600-3200 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, J = 6.5 Hz, 3 H), 1.66 (s, 1 H), 3.71 (s, 3 H), 5.01 (q, J = 6.5 Hz, 1 H), 6.93-6.99 (m, 2 H), 7.18-7.27 (m, 3 H), 7.30 (dt, J = 7.2, 1.2 Hz, 1 H), 7.40 (dt, J = 7.2, 1.5 Hz, 1 H), 7.66 (dd, J = 7.8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.9 (q'), 55.3 (q'), 66.5 (d'), 113.6 (d'), 125.3 (d'), 127.1 (d'), 127.8 (d'), 130.2 (d'), 130.4 (d'), 133.3 (s'), 140.1 (s'), 143.3 (s'), 158.8 (s'); exact mass m/z calcd for $C_{15}H_{16}O_2$ 228.1150, found 228.1152.

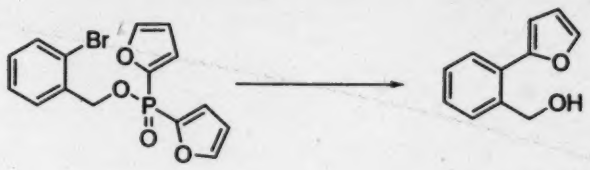
Methyl 2'-(1-Hydroxyethyl)[1,1'-biphenyl]-4-carboxylate (47.4).



47.3 **47.4**

The general procedure for radical aryl transfer was followed, using phosphinate **47.3** (0.183 g, 0.35 mmol) in PhMe (20 mL), and Bu_3SnH (0.206 g, 0.71 mmol) and AIBN (0.029 g, 0.18 mmol) in PhMe (15 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **47.4** (0.049 g, 54%) as a white solid: mp 97-98 °C; FTIR (CH_2Cl_2 cast) 3600-3100, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (d, J = 6.5 Hz, 3 H), 1.89 (s, 1 H), 3.94 (s, 3 H), 4.93 (q, J = 6.5 Hz, 1 H), 7.16-7.21 (m, 1 H), 7.29-7.48 (m, 4 H), 7.69 (dd, J = 7.8, 1.8 Hz, 1 H), 8.04-8.11 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0 (q'), 52.2 (q'), 66.4 (d'), 125.5 (d'), 127.3 (d'), 128.5 (d'), 129.0 (s'), 129.4 (d'), 129.5 (d'), 129.6 (d'), 139.3 (s'), 143.0 (s'), 145.8 (s'), 167.0 (s'); exact mass m/z calcd for $C_{16}H_{16}O_3$ 256.1100, found 256.1105.

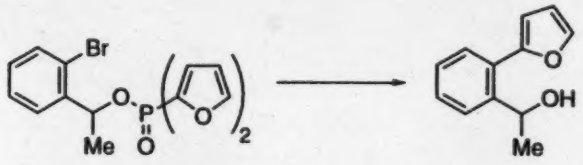
2-(2-Furanyl)benzenemethanol (48.5a).



48.4a **48.5a**

The general procedure for radical aryl transfer was followed, using phosphinate **48.4a** (0.227 g, 0.62 mmol) in xylene (30 mL), and Ph_3SnH (0.435, 1.24 mmol) and AIBN (0.051 g, 0.31 mmol) in xylene (20 mL). The solvent was evaporated, and the residue was dissolved in *t*-BuOH (ca 10 mL). $NaCNBH_3$ (0.081 g, 1.29 mmol) was added and the mixture was refluxed for 1 h.[9] Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **48.5a**[56] (0.048 g, 44%) as a white solid: mp 68-69 °C; FTIR (CH_2Cl_2 cast) 3500-3000 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.77 (s, 1 H), 4.79 (s, 2 H), 6.52 and 6.54 (apparent doublets, J = 1.8 Hz, 1 H in all), 6.67 and 6.69 (apparent doublets, J = 0.9 Hz, 1 H in all) (the signals at 6.52 and 6.54, and at 6.67 and 6.69 correspond to part of an ABX system), 7.29-7.42 (m, 2 H), 7.46-7.57 (m, 2 H), 7.62-7.70 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 64.3 (t'), 108.7 (d'), 111.7 (d'), 127.8 (d'), 128.1 (d'), 128.1 (d'), 129.4 (d'), 129.7 (s'), 137.2 (s'), 142.5 (d'), 153.2 (s'); exact mass m/z calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0679.

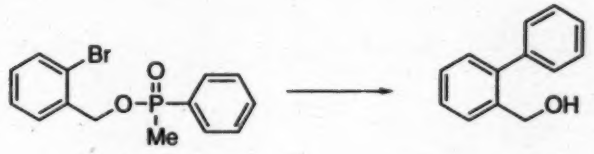
2-(2-Furanyl)-α-methylbenzenemethanol (48.5b).



48.4b **48.5b**

The general procedure for radical aryl transfer was followed, using phosphinate **48.4b** (0.125 g, 0.33 mmol) in xylene (20 mL), and Ph_3SnH (0.232 g, 0.66 mmol) and AIBN (0.027 g, 0.16 mmol) in xylene (15 mL). The solvent was evaporated, and the residue was dissolved in *t*-BuOH (ca 10 mL). $NaCNBH_3$ (0.058 g, 0.92 mmol) was added and the mixture was refluxed for 1 h.[9] Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **48.5b**[57] (0.0105 g, 17%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3600-3200 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (d, J = 6.8 Hz, 3 H), 1.62 (s, 1 H), 5.30 (q, J = 6.8 Hz, 1 H), 6.50-6.53 (m, 2 H), 7.20 (dt, J = 7.5, 1.8 Hz, 1 H), 7.40 (dt, J = 7.8, 1.8 Hz, 1 H), 7.51-7.55 (m, 2 H), 7.71 (dd, J = 7.8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.2 (q'), 66.8 (d'), 108.8 (d'), 111.4 (d'), 125.7 (d'), 127.4 (d'), 128.60 (d'), 128.64 (d'), 128.8 (s'), 142.4 (d'), 143.2 (s'), 153.4 (s'); exact mass m/z calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0831.

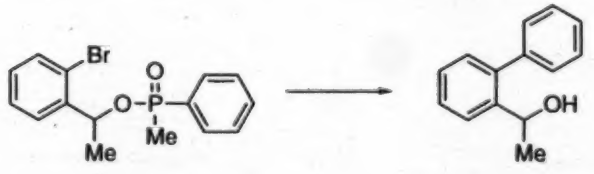
[1,1'-Biphenyl]-2-methanol (43.3a).



53.4a **43.3a**

The general procedure for radical aryl transfer was followed, using phosphinate **53.4a** (0.173 g, 0.53 mmol) in PhMe (30 mL), and Bu_3SnH (0.310 g, 1.06 mmol) and AIBN (0.044 g, 0.27 mmol) in PhMe (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **43.3a** (0.027 g, 27%) as a colorless oil, identical with material obtained from **43.2a**.

α-Methyl[1,1'-biphenyl]-2-methanol (43.3b).

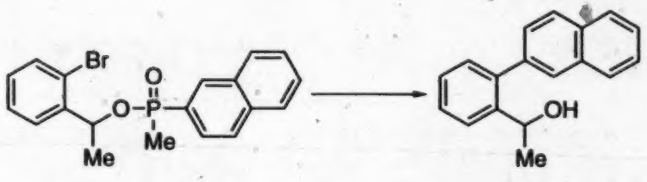


53.4b **43.3b**

The general procedure for radical aryl transfer was followed, using phosphinates **53.4b** (0.174 g, 0.51 mmol) in PhMe (30 mL), and Bu_3SnH (0.299 g, 1.03 mmol) and AIBN (0.042 g, 0.26 mmol) in PhMe (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave

43.3b (0.074 g, 73%) as a white solid (mp 109-110 °C), identical to material obtained from **43.2b**.

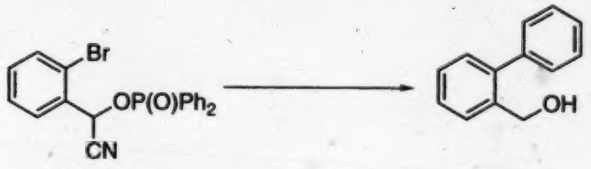
α-Methyl[2-(2-naphthalenyl)phenyl]methanol (56.1).



54.6 **56.1**

The general procedure for radical aryl transfer was followed, using phosphinates **54.6** (0.136 g, 0.35 mmol) in xylene (20 mL), and Ph_3SnH (0.245 g, 0.70 mmol) and AIBN (0.028 g, 0.17 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **56.1** (0.061 g, 70%) as a white solid: mp 145-146 °C; FTIR (CH_2Cl_2 cast) 3500-3100 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.43 (d, J = 6.5 Hz, 3 H), 1.72 (s, 1 H), 5.05 (q, J = 6.5 Hz, 1 H), 7.29-7.39 (m, 2 H), 7.43-7.57 (m, 2 H), 7.70-7.80 (m, 4 H), 7.84-7.94 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.0 (q'), 66.6 (d'), 125.4 (d'), 126.1 (d'), 126.4 (d'), 127.2 (d'), 127.69 (d'), 127.73 (d'), 127.99 (d'), 128.02 (d'), 128.1 (d'), 130.2 (d'), 132.4 (s'), 133.2 (s'), 138.5 (s'), 140.3 (s'), 143.3 (s'); exact mass m/z calcd for $C_{18}H_{16}O$ 248.1201, found 248.1200.

[1,1'-Biphenyl]-2-methanol (43.3a).



57.2 **43.3a**

The general procedure for radical aryl transfer was followed, using phosphinate **57.2** (0.134 g, 0.33 mmol) in xylene (20 mL), and Ph_3SnH (0.231 g, 0.66 mmol) and AIBN (0.028 g, 0.17 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **43.3a** (0.017 g, 28%) as a colorless oil, identical with material obtained from **43.2a**. A small amount (13%) of simple reduction product (replacement of Br by H in **57.2**) was also isolated: ^1H NMR ($CDCl_3$, 360 MHz) δ 6.21 (d, J = 10.0 Hz, 1 H), 7.35-7.45 (m, 5 H), 7.48-7.58 (m, 5 H), 7.58-7.74 (m, 3 H), 7.87-7.95 (m, 2 H).

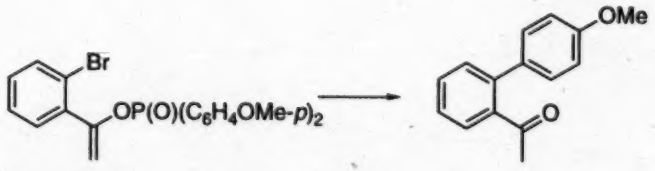
1-[1,1'-Biphenyl]-2-ylethanone (58.4).

58.3 **58.4**

The general procedure for radical aryl transfer was followed, using phosphinate **58.3** (0.185 g, 0.46 mmol) in

xylene (20 mL), and Ph_3SnH (0.325 g, 0.93 mmol) and AIBN (0.038 g, 0.23 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **58.4**[53] (0.064 g, 70%) as a light yellow liquid: FTIR (CH_2Cl_2 cast) 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.01 (s, 3 H), 7.32-7.58 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 30.4 (q'), 127.5 (d'), 127.9 (two overlapping signals) (d'), 128.7 (d'), 128.9 (d'), 130.3 (d'), 130.7 (d'), 140.5 (s'), 140.8 (s'), 140.9 (s'), 204.8 (s'); exact mass *m/z* calcd for $C_{14}H_{12}O$ 196.0888, found 196.0888.

1-(4'-Methoxy[1,1'-biphenyl]-2-yl)ethanone (59.3).



59.2 **59.3**

The general procedure for radical aryl transfer was followed, using phosphinate **59.2** (0.193 g, 0.42 mmol) in xylene (20 mL), and Ph_3SnH (0.295 g, 0.84 mmol) and AIBN (0.028, 0.17 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **59.3**[58] (0.065 g, 68%) as a light yellow liquid: FTIR (CH_2Cl_2 cast) 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.01

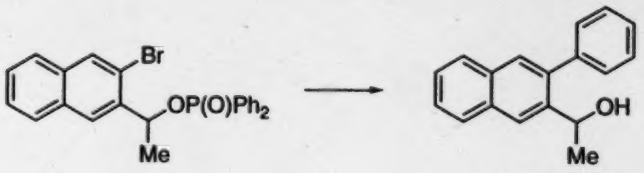
(s, 3 H), 3.83 (s, 3 H), 6.94-7.00 (m, 2 H), 7.24-7.30 (m, 2 H), 7.35-7.42 (m, 2 H), 7.46-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 36.5 (q'), 58.1 (q'), 109.2 (d'), 120.4 (d'), 121.1 (d'), 123.0 (d'), 123.1 (d'), 123.6 (d'), 125.6 (s'), 131.8 (s'), 132.5 (s'), 148.7 (s'), 188.4 (s'); exact mass *m/z* calcd for $C_{15}H_{14}O_2$ 226.0994, found 226.1000.

2-Phenyl-3-pyridinemethanol (61.2).

61.1 **61.2**

The general procedure for radical aryl transfer was followed, using phosphinate **61.1** (0.194 g, 0.50 mmol) in xylene (20 mL), and Bu_3SnH (0.316 g, 1.09 mmol) and AIBN (0.045 g, 0.27 mmol) in xylene (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 2:3 EtOAc-hexane, gave **61.2** (0.038 g, 41%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3500-3000 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 1 H), 4.69 (s, 2 H), 7.34 (dd, *J* = 7.5, 4.5 Hz, 1 H), 7.40-7.50 (m, 3 H), 7.52-7.56 (m, 2 H), 7.42-7.88 (m, 1 H), 8.63 (dd, *J* = 5.0, 2.0 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 62.4 (t'), 122.7 (d'), 128.5 (d'), 128.6 (d'), 129.3 (d'), 134.3 (s'), 136.7 (d'), 140.2 (s'), 148.7 (d'), 158.2 (s'); exact mass *m/z* calcd for $C_{12}H_{11}NO$ 185.0841, found 185.0840.

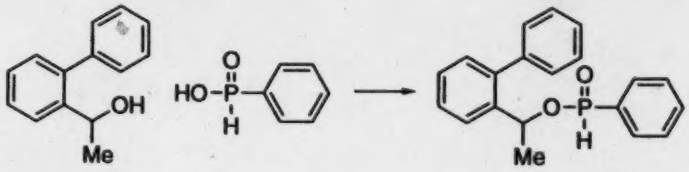
α-Methyl(3-phenyl-2-naphthalene)methanol (67.4).



67.3 **67.4**

The general procedure for radical aryl transfer was followed, using phosphinate **67.3** (0.189 g, 0.42 mmol) in PhH (20 mL), and Ph_3SnH (0.294 g, 0.84 mmol) and AIBN (0.034 g, 0.21 mmol) in PhH (20 mL). Evaporation of the solvent after KF treatment, and flash chromatography of the residue over silica gel (1.8 x 25 cm), using 1:10 EtOAc-hexane, gave **67.4** (0.026 g, 25%) as a light yellow solid: mp 100-101 °C; FTIR (CH_2Cl_2 cast) 3500-3100, 3054, 3022, 2971, 2926 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.45 (d, J = 6.5 Hz, 3 H), 1.70 (s, 1 H), 5.14 (q, J = 6.5 Hz, 1 H), 7.37-7.53 (m, 7 H), 7.68 (s, 1 H), 7.79-7.85 (m, 1 H), 7.88-7.93 (m, 1 H), 8.12 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0 (q'), 66.8 (d'), 124.1 (d'), 126.1 (d'), 126.2 (d'), 127.2 (d'), 127.6 (d'), 127.8 (d'), 128.2 (d'), 128.9 (d'), 129.5 (d'), 132.4 (s'), 132.9 (s'), 139.0 (s'), 140.9 (s'), 141.9 (s'); exact mass m/z calcd for $C_{18}H_{16}O$ 248.1201, found 248.1202.

1-[1,1'-Biphenyl]-2-ylethyl Phenylphosphinate (76.5).



43.3b **76.5**

Solid PhPH(O)OH[40] (0.037 g, 0.26 mmol) was added to a stirred solution of α-methyl[1,1'-biphenyl]-2-methanol (**43.3b**) (0.026 g, 0.13 mmol) and DMAP (ca 6 mg, 0.05 mmol) in THF (10 mL). Stirring was continued for ca 10 min, and then DCC (0.054 g, 0.26 mmol) was added. After 1 h, the mixture was filtered, and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.3 x 20 cm), using 1:1 EtOAc-hexane, gave a mixture of two diastereoisomers of 1-[1,1'-biphenyl]-2-ylethyl phenylphosphinate (**76.5**) (0.025 g, 60%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3058, 3025, 2980, 2929, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.58 (d, J = 6.5 Hz, 3 H), 5.50 (dq, J = 10.0, 6.5 Hz, 0.45 H), 5.71 (dq, J = 10.0, 6.5 Hz, 0.52 H), 7.35 (d, J = 556 Hz, 0.52 H), 7.54 (d, J = 569 Hz, 0.46 H), 6.94-7.61 (m, 12 H), 7.66-7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0 (d, J = 4.3 Hz, q'), 25.2 (d, J = 3.7 Hz, q'), 72.0 (d, J = 5.9 Hz, d'), 72.9 (d, J = 5.9 Hz, d'), 126.1 (d'), 127.2 (d'), 127.5 (d'), 127.7 (d'), 127.9 (d'), 128.1 (d'), 128.2 (d'), 128.5 (d'), 128.67 (d'), 128.71 (d'), 129.0 (d'), 129.1 (d'), 129.8 (d'), 130.1 (d'), 130.7 (d'), 130.9

(d'), 131.0 (d'), 131.2 (d'), 132.81 (d'), 132.84 (d'), 132.87 (d'), 132.90 (d'), 138.93 (s'), 138.98 (s'), 139.40 (s'), 139.47 (s'), 139.9 (s'), 140.0 (s'), 140.1 (s'), 140.6 (s'); exact mass *m/z* calcd for $C_{20}H_{19}O_2P$ 322.1123, found 322.1118.

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Chapter 2

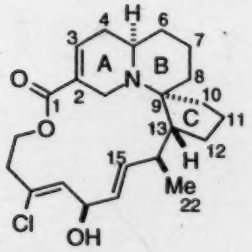
Synthetic studies related to halichlorine

Introduction

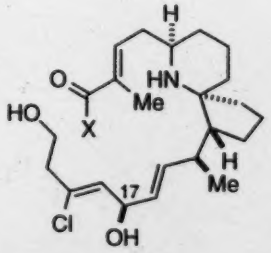
Marine natural products have been extensively studied for several decades,[1] and they continue to hold a unique fascination, not only because of their relationship to the organisms from which they are derived, and because of their potential usefulness to man in their natural form or as templates for synthetic analogs, but chiefly because each new structural type reveals something of nature's molecular architecture and poses new questions of how and why these compounds are being produced. Marine alkaloids comprise an enormous group of marine natural products with very diverse structures. The useful biological properties possessed by many alkaloids, coupled with their interesting and challenging structures, make them targets for extensive synthetic studies.

Halichlorine (**1.1**), pinnaic acid (**1.2**) and tauropinnaic acid (**1.3**) are structurally related natural products recently isolated from marine organisms by Uemura and coworkers.[2,3]

Scheme 1



1.1



1.2 X = OH
1.3 X = $NHCH_2CH_2SO_3H$

Their biological properties may establish them as important lead compounds for the design of anti-inflammatory drugs.

Halichlorine, a novel alkaloid, was isolated from the marine sponge *Halichondria okadai Kadota* collected in a mediolittoral zone in Kanagawa Prefecture.[2] It inhibits the expression of vascular cell adhesion molecule-1 (VCAM-1) at IC_{50} 7 μg/mL.[4] VCAM-1, a member of the immunoglobulin superfamily, monitors and regulates leukocyte recruitment into inflamed tissue.[5] Since leukocyte infiltration is involved in various allergic inflammatory disorders, as well as pathogenic processes such as asthma and arteriosclerosis, VCAM-1 has emerged as a potential target for drug discovery. In principal, blockade or inhibition of VCAM-1 could be useful in regulating leukocyte trafficking. Given such considerations, an agent that specifically inhibits induced VCAM-1 expression could be of particular value, and for this reason, halichlorine commands particular attention.

The pinnaic acids, isolated from the Okinawan bivalve *Pinna muricata*, are inhibitors of phospholipase A_2 (PLA_2). Such inhibitors have been considered to be potential drugs for the treatment of inflammation,[3] because PLA_2 is linked to the initial step in the cascade of enzymatic reactions which leads to the generation of inflammatory mediators.[6] Pinnaic acid and tauropinnaic acid exhibited inhibitory activity with a cytosolic 85-kDa phospholipase, with IC_{50} values of 0.2 mM and 0.09 mM, respectively.[7a] Cytosolic 85-kDa phospholipase ($cPLA_2$) is an important member of the PLA_2 family, since it

plays a significant role in the generation of free arachidonic acid from the *sn*-2 position of cellular phopholipids in most mammalian cells.[7b,c] The released arachidonic acid can mediate the biosynthesis of eicosanoids, prostaglandins, leukotrienes, and thromoboxanes.[8] These biological messengers govern critical phenomena such as cell proliferation and inflammatory responses. Therefore, compounds that inhibit $cPLA_2$ activity are promising targets for the development of novel anti-inflammatory drugs.

The relative stereochemistry of halichlorine was determined by an extensive analysis of coupling constants and a NOESY spectrum,[2] and the absolute configuration was established by oxidative degradation, followed by asymmetric synthesis of the degradation product.[9] Halichlorine is a 15-membered macrolactone with 23 carbons in total, containing 5 stereogenic centers, of which three [C(9), C(13), C(14)] are contiguous. The most fascinating structure in halichlorine and pinnaic acids is the 6-azaspiro[4,5]decane core. Pinnaic acids have the same carbon skeleton as halichlorine except for the absence of the tetrahydropyridine ring and the macrolactone. The configurations of C(14) and C(17) were not conclusively assigned due to the small quantities of pinnaic acids available through isolation by Uemura.[3] However, Danishefsky and coworkers recently provided rigorous evidence for the indicated stereochemistry (**1.2** and **1.3**) of the natural pinnaic acids by a combination of total synthesis and chemical degradation.[10e]

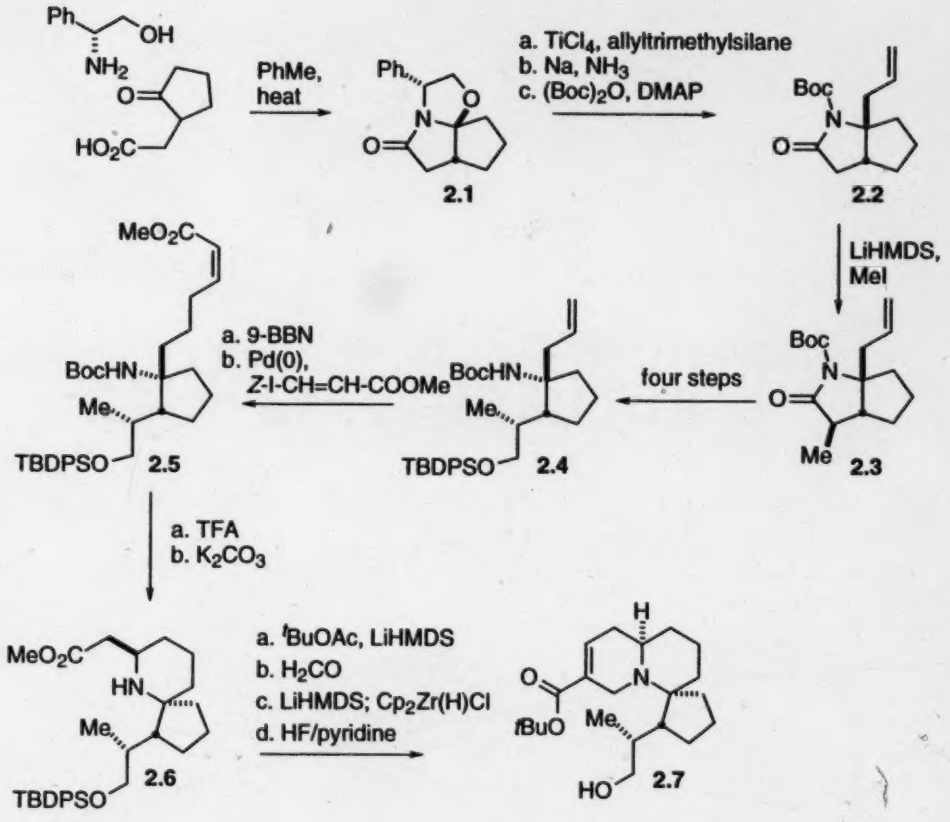
The interesting biological activities, as well as the unusual architectural features of halichlorine and the pinnaic acids, attracts synthetic chemists to devise routes for their total synthesis. Synthetic work related to halichlorine and pinnaic acids, including studies on methods for constructing the 1,4-diene side chain[11] and the spirobicyclic core,[10a,12-18] have appeared since 1999, and a total synthesis of halichlorine and pinnaic acid has been finished by Danishefsky.[10c,e] These synthetic studies are summarized in the following sections.

Synthetic review

Total synthesis of halichlorine and pinnaic acids by Danishefsky

Danishefsky's stereocontrolled synthesis of halichlorine[10a,b] started from the Meyers lactam **2.1**. The lactam was treated with an excess of allyltrimethylsilane in the presence of $TiCl_4$, and the product was subsequently converted into **2.2** by Sakurai methodology. Stereoselective methylation from the less hindered convex face of the cup-like structure **2.2** gave **2.3**. The five-membered lactam was then opened to provide **2.4**. Hydroboration, followed by Suzuki-coupling, afforded the unsaturated ester **2.5**. At this point, unmasking of the primary amine set the stage for a stereoselective Michael addition, which gave the azaspirobicyclic core containing four of the stereogenic

Scheme 2



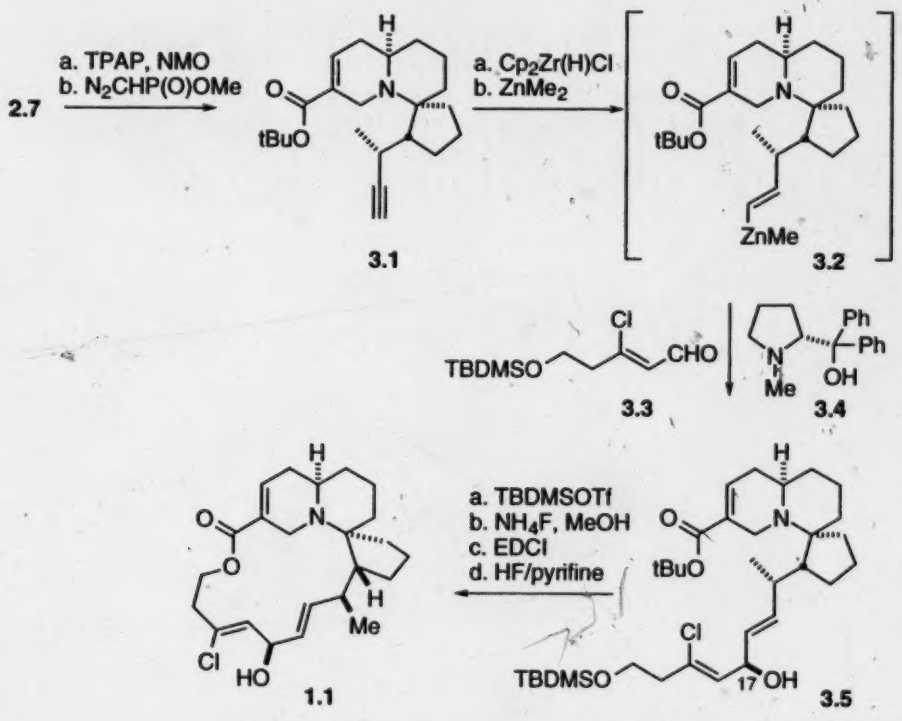
centers needed to reach halichlorine.

The tetrahydropyridine was constructed from **2.6** by a crossed Claisen-intramolecular Mannich sequence, followed by application of Ganem's protocol. Deprotection with HF-pyridine then afforded the primary alcohol **2.7**.

Treatment of **2.7** with TPAP and an excess of NMO, followed by reaction with Gilbert's reagent, produced alkyne **3.1**. Hydrozirconation and metal exchange with dimethylzinc gave the vinylzinc **3.2**. This underwent coupling with

aldehyde **3.3**, prepared from the corresponding Weinreb amide, in the presence of Soai's chiral amino alcohol **3.4**, yielding a 4:1 mixture of the desired 17*R*-diastereomer **3.5**.

Scheme 3

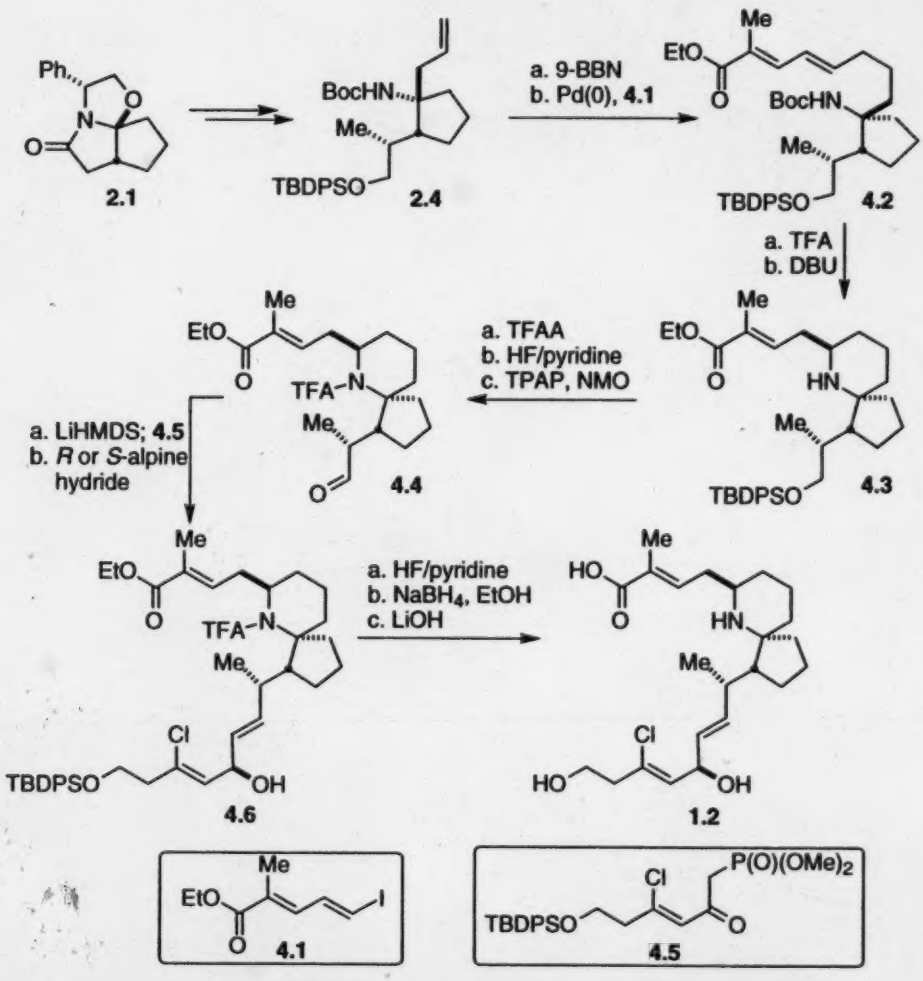


The total synthesis of halichlorine was completed by four more steps: silylation, selective cleavage of the primary *t*-$BuMe_2Si$ group, macrolactonization, and deprotection of the silylated secondary alcohol.

For the total synthesis of pinnaic acid,[10d,e] Danishefsky's approach started from the same Meyers' lactam **2.1**, which was converted to the protected amino alcohol **2.4**,

as shown in Scheme 2. Coupling the alkylborane derived from **2.4** with vinyl iodide **4.1** generated **4.2**. The formation of the azaspirobicyclic core was completed through deprotection and intramolecular vinylogous (1,6-addition) Michael reaction (**4.2**→**4.3**). Amino group protection with trifluoroacetic anhydride, followed by silyl group deprotection and

Scheme 4



oxidation, then afforded **4.4**. Remarkably, base mediated reaction of aldehyde **4.3** with the known phosphonate **4.5**, followed by hydride reduction with *R*- or *S*-Alpine borane, produced optically pure **4.6**. Removal of the silyl group from **4.6** and cleavage of the trifluoroacetyl and ethyl ester functions completed the total synthesis of pinnaic acid. The high field NMR spectrum of the final product was similar to that reported by Uemura and coworkers for the natural product. The stereochemistry at C(14) and C(17) was rigorously deduced by synthesis of four possible isomers of pinnaic acid, and it was established that the natural stereochemistry is 14*S*,17*R*, as shown in **1.2**, which is the same as at the corresponding positions of halichlorine. It is noteworthy that alcohol **4.6** with the *R* configuration is formed through a highly stereoselective reduction. This stereoselectivity is not dependent on the chirality of the reducing reagent (Alpine borane), but results from a so-called long-range stereochemical transmission by the methyl group at C(14) and the total molecular environment of the spirocyclic ring system.

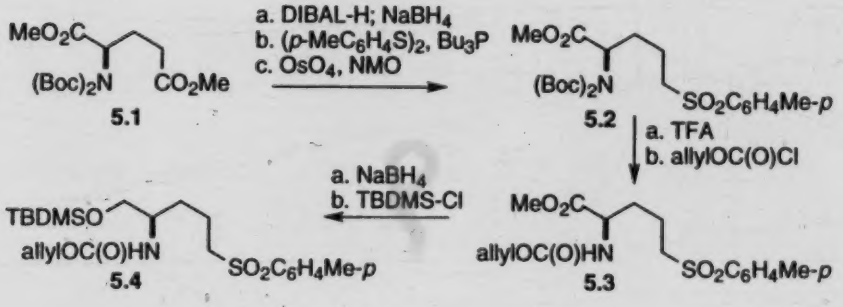
Clive's approach to the azaspirobicyclic core

The approach[12] followed in this laboratory is based on the linking of two subunits **5.4** and **6.4**, followed by radical cyclization to generate the spirobicyclic core.

Construction of the first subunit started from diester **5.1**, which was obtained from D-glutamic acid. Reduction with

DIBAL-H and then $NaBH_4$ and subsequent sulfonation generated sulfone **5.2**. The protecting group on the nitrogen was changed from Boc to allyloxycarbonyl. Finally, the ester was reduced, and the resulting alcohol was protected as its silyl ether to give the first subunit **5.4**.

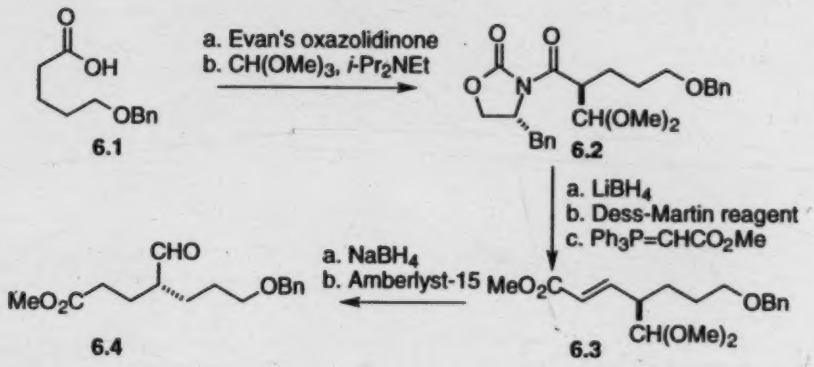
Scheme 5



The second component was made from acid **6.1**, readily available from δ-valerolactone. Acylation of Evans's oxazolidinone and alkylation with trimethyl orthoformate produced **6.2**. The stereochemistry of **6.2** was assigned by analogy with a related alkylation and was confirmed by X-ray analysis of a later intermediate. The chiral auxiliary was removed, and homologation of the liberated alcohol by Dess-Martin oxidation and Wittig olefination gave the unsaturated ester **6.3**. Saturation of the double bond and acid-catalyzed hydrolysis of the acetal to an aldehyde gave the final subunit **6.4**.

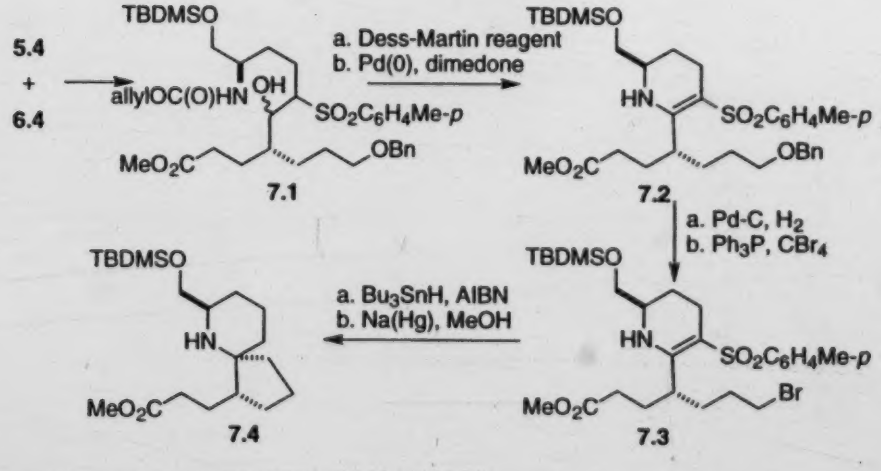
The subunits **5.4** and **6.4** were linked to generate the diastereoisomeric hydroxy sulfones **7.1**. Oxidation and

Scheme 6



removal of the allyloxycarbonyl group produced the desired sulfonyl enamine **7.2**. Finally, debenzylation and replacement of the liberated hydroxyl generated the radical precursor **7.3**. It was subjected to standard conditions for radical cyclization and yielded the desired spirocycle. Final desulfonylation gave the 6-azaspiro[4,5]decane **7.4**.

Scheme 7

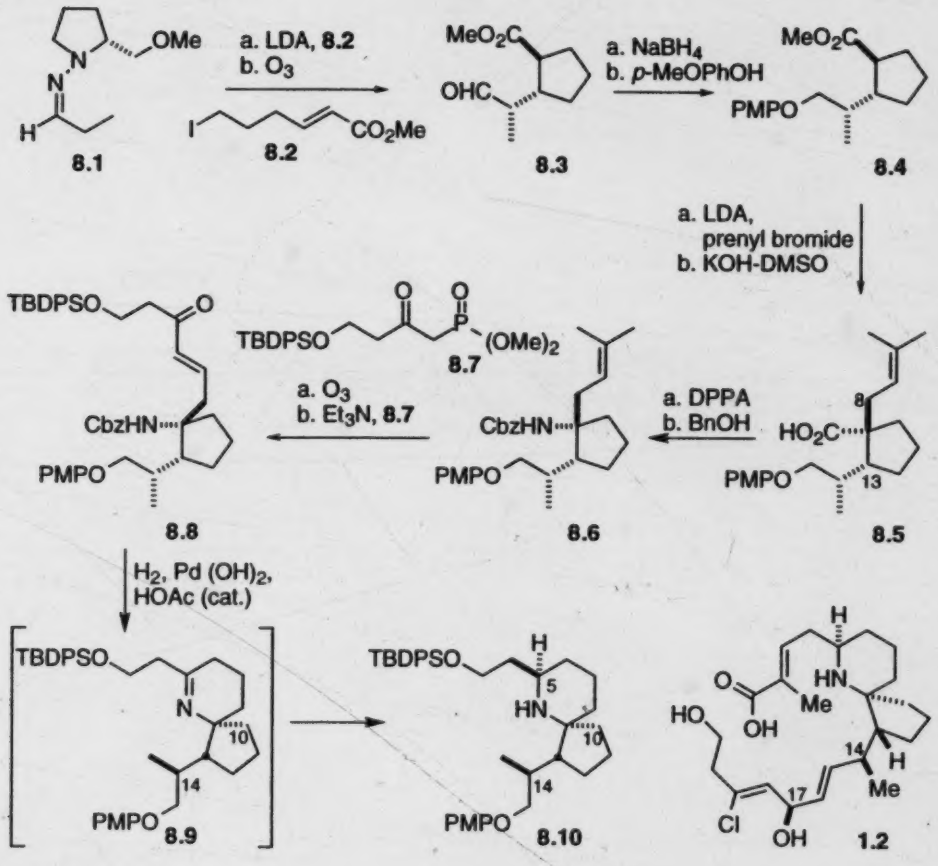


representing the core of halichlorine and the pinnaic acids.

Arimoto's approach to the spirobicyclic core of pinnaic acid

This approach was based on an asymmetric Michael-initiated ring closure (MIRC) reaction.[13] The synthetic study started from hydrazone **8.1**, which was treated with LDA then with the Michael acceptor **8.2**. The desired aldehyde **8.3** was obtained as a single isomer after oxidative removal of the auxiliary by ozonolysis. Reduction and protection under Mitsunobu conditions then provided ester **8.4**. Alkylation of the ester enolate with prenyl bromide occurred with complete facial selectivity from the β-side, as expected due to the shielding of α-side by the chain at C(13). The stereochemical assignment was supported by observation of an NOE between protons of C(8) and C(13). The carboxylic acid generated by base hydrolysis was converted into **8.6** by Curtius rearrangement and subsequent protection. Ozonolysis and Horner-Emmons-Wadsworth olefination provided the MIRC precursor **8.8**. Removal of the Cbz group from **8.8** and reduction of the resultant imine **8.9** were achieved simultaneously under the hydrogenolysis conditions in the presence of a catalytic amount of acetic acid. Observation of an NOE between the protons of C(5) and C(10) suggested that the hydrogenation proceeded exclusively from the desired α-face – a result that could be rationalized by the hindrance at C(13) preventing approach of the palladium catalyst from

Scheme 8



β-face.

However, the stereochemistry at C(14) of compound **8.10** is different from that deduced by Danishefsky for **1.2**, as reviewed above.

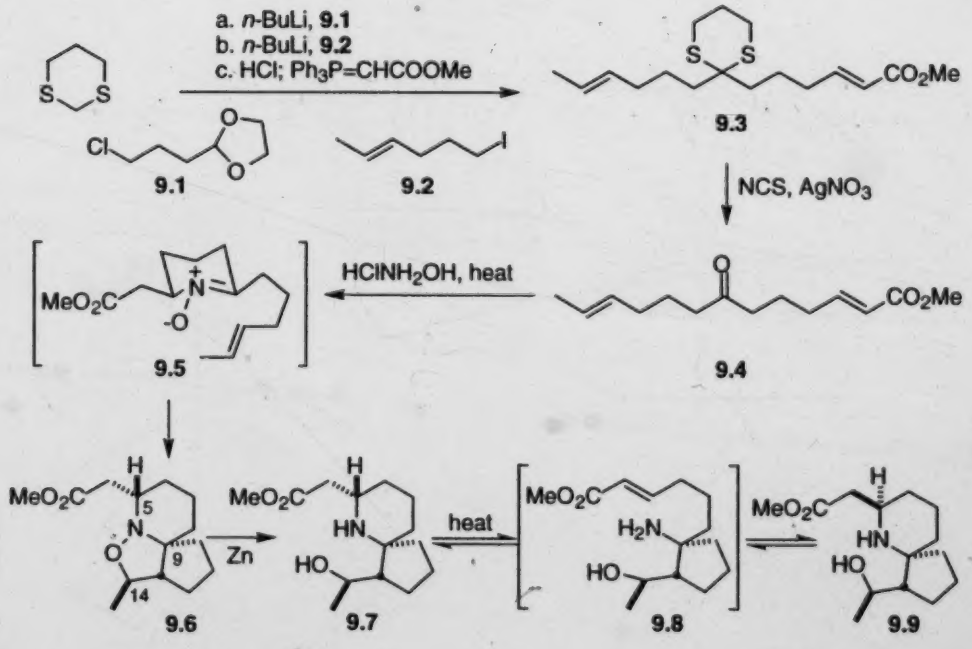
Zhao's stereospecific preparation of the azaspirobicyclic core

This approach[14] was based on a tandem cyclization

(Michael addition and 1,3-dipolar cycloaddition) via **9.5**. This tandem sequence set up three stereogenic centers [C(9), C(13) and C(14)] of halichlorine. The stereochemistry of C(5) was set by thermal isomerization (**9.7→9.9**).

The route started with sequential alkylation of 1,3-dithiane with alkyl chloride **9.1** and alkyl iodide **9.2** to generate the dialkylated adduct, which was selectively hydrolyzed and subsequently treated with a Wittig reagent so as to form the unsaturated ester **9.3**. Oxidative hydrolysis of **9.3** with NCS in the presence of silver nitrate yielded ketone **9.4**, which was heated with hydroxylamine hydrochloride, following Grigg's methodology for tandem

Scheme 9



intramolecular cycloaddition. In this case, the process proceeded through intermediate **9.5** to generate **9.6** as the sole diastereomer with the required stereochemistry for the synthesis of halichlorine, except at C(5).

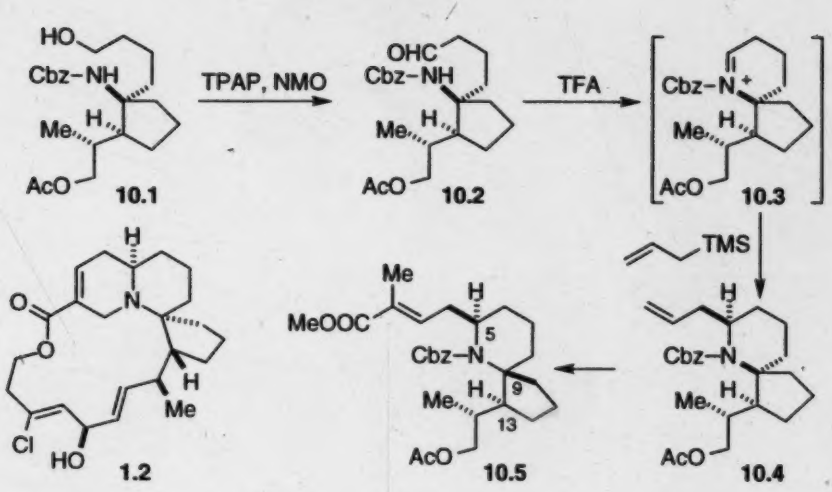
Reductive cleavage of the nitrogen-oxygen bond in **9.6** with zinc afforded amino alcohol **9.7**, which was equilibrated under thermal conditions to invert the stereochemistry at C(5) via retro-Michael addition to intermediate **9.8** and reclosure, so as to give the thermodynamically more stable isomer **9.9**. The stereochemistry of **9.9** was supported by NOE studies.

Forsyth's *in situ* iminium ion formation-allylation approach towards the azaspirobicyclic core

This approach[15] provided a route to the spirobicyclic core. However, the absolute configurations at C(9) and C(13) in **10.5** turned out to be opposite to those in halichlorine and the pinnaic acids.

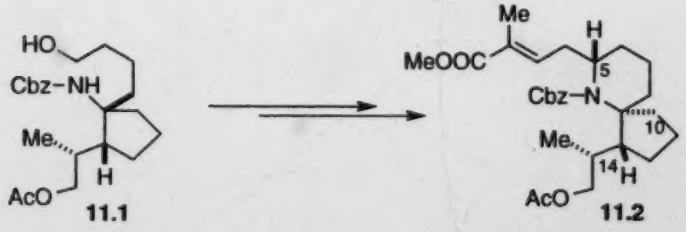
This methodology started from the highly functionalized synthetic intermediate **10.1**, whose synthesis has not yet been published. TFA treatment of aldehyde **10.2**, generated by TPAP oxidation, led to sequential condensation and imminium ion formation. Upon addition of allyltrimethylsilane, allyl addition occurred, and a single diastereomer (**10.4**) was obtained. The C(1)–C(4) side chain corresponding to halichlorine was elaborated by oxidation of the double bond in **10.4**, followed by Wittig olefination, to give **10.5**. NOEs

Scheme 10



measured with compound **10.5** were observed between protons at C(4) and C(10), and between C(5) and the methyl group at C(14). These observations indicated the facial selectivity of the allylation, the result being similar to that observed by Arimoto in the hydride delivery, and was again due to the fact that the side chain at C(13) prevents allyl attack from the β-face. As mentioned above, the stereochemistry at C(9) and C(13) was opposite to that in halichlorine.

Scheme 11



Even if the synthetic route were to start with compound **11.1** having the correct absolute configurations at C(9), C(13) and C(14), the final product obtained by the above route would be compound **11.2**, in which the stereochemistry at C(5) is epimeric to that in halichlorine. Therefore, further work is required if this approach to halichlorine is to succeed.

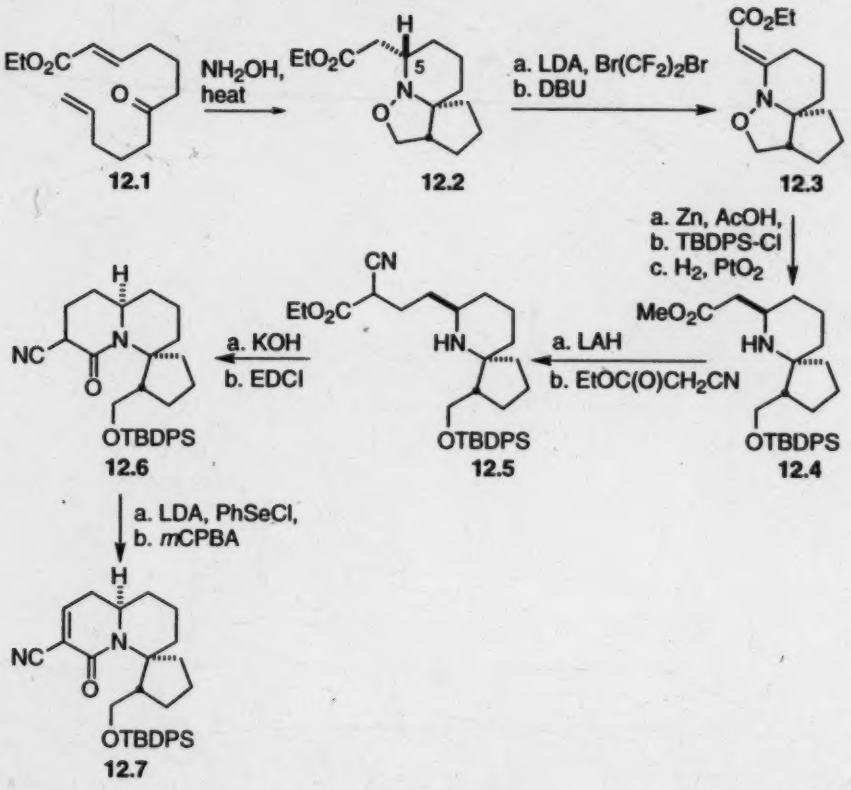
Shishido's approach to the tricyclic core of halichlorine

Shishido's approach[16] to the tricyclic core of halichlorine started from Grigg's tricyclic isoxazolidine **12.2**, and is similar to Zhao's approach, reviewed above. Intramolecular Michael addition of the initially-formed oxime from **12.1**, followed by [3+2] dipolar cycloaddition of the resulting six-membered cyclic nitrone gave **12.2**.

The correct stereochemistry at C(5) was set up in five steps, including double bond formation to give **12.3**, hydroxyl protection with a bulky silyl group, and facially selective hydrogenation. Reduction of **12.4** with $LiAlH_4$, and Tsunoda-Mitsunobu coupling, provided cyano ester **12.5**. Lactam **12.6** was obtained by hydrolysis and EDCI-mediated coupling. The desired tricyclic core (**12.7**) of halichlorine was generated by phenylselenation and oxidative elimination.

This approach takes the sequence closer to halichlorine than the experiments in Zhao's study.

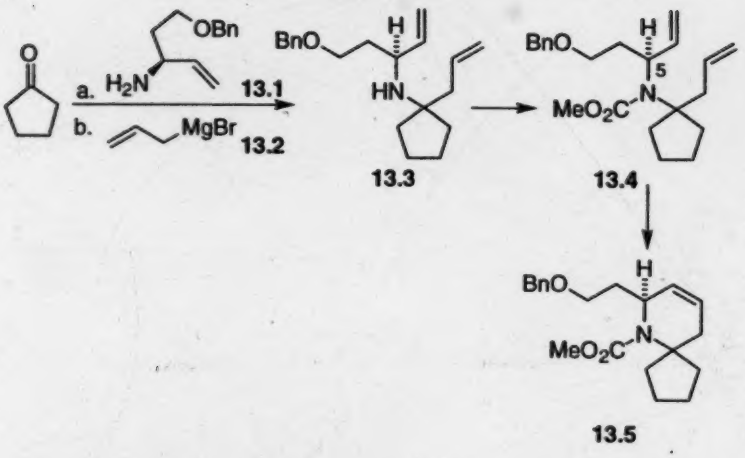
Scheme 12



Wright's ring-closing metathesis approach to the spirobicyclic core

This approach to the spirobicyclic core of halichlorine and the pinnaic acids is based on an imine alkylation/ring closing metathesis sequence.[17] Cyclopentanone was treated with amine **13.1**, generated from methionine. The resulting imine was reacted with allylmagnesium bromide to afford diene **13.3**. The ring closing metathesis was improved, using less catalyst and a shorter reaction time, when the secondary amine nitrogen was protected by acylation, as in **13.4**.

Scheme 13

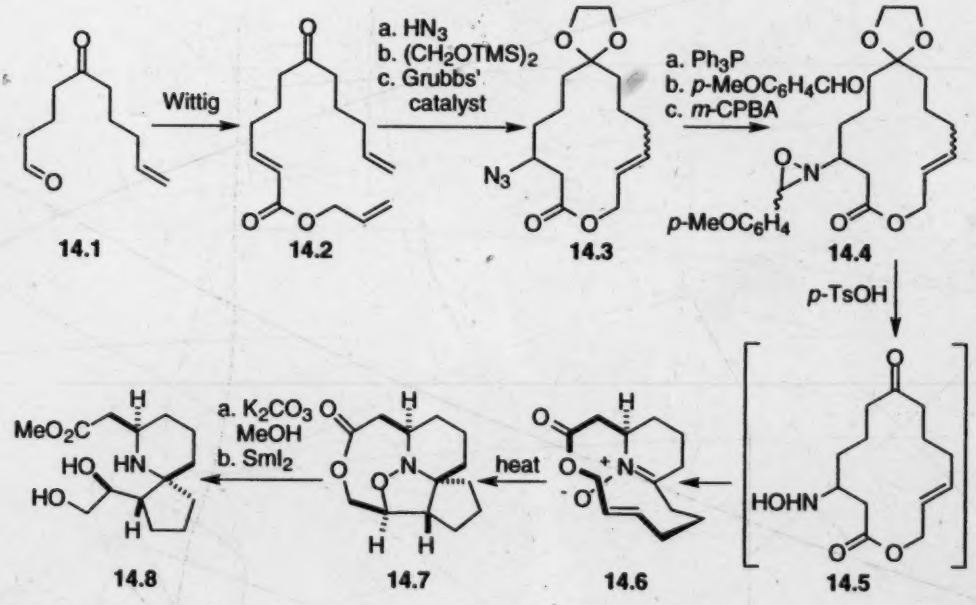


White's transannular nitrone cycloaddition to the spirobicyclic core

White's transannular nitrone cycloaddition methodology[18] was demonstrated to be applicable to a stereocontrolled synthesis of the azaspirobicyclic core of halichlorine and the pinnaic acids. The route started from aldehyde **14.1**, prepared from cyclopentanone in four steps. Wittig reaction produced the trans allylic ester **14.2**. Conjugate addition, ethylene ketal formation and Grubbs' ring-closing metathesis afforded an inseparable mixture of 14-membered macrocyclic alkene isomers which would be separated at a later stage. Oxaziridine **14.4** was then made in three steps by iminophosphorane formation, aza-Wittig condensation and selective oxidation. Hydrolysis of the ethylene ketal and the oxaziridine occurred simultaneously under acidic conditions to give the keto hydroxylamine intermediate **14.5**,

which underwent spontaneous intramolecular condensation to produce nitrone **14.6**. The minor *Z* isomer was removed at this stage by careful column chromatography. A single crystalline product (**14.7**) was obtained from nitrone **14.6** in refluxing PhMe. Finally, base-catalyzed methanolysis and reductive cleavage yielded the dihydroxy amino ester **14.8**, containing three stereogenic centers [(C(5), C(9) and C(13)] of the azaspirobicyclic core of halichlorine.

Scheme 14



The stereochemistry was confirmed by X-ray analysis of compound **14.7**. It was presumed that the ring size was an important requirement for the stereocontrol observed in the transannular nitrone cycloaddition. The ring size had to be

large enough to permit flexibility in the approach of the nitrone to its olefin partner, but not so large as to allow the nitrone oxygen to pass through the plane of the macrocycle.

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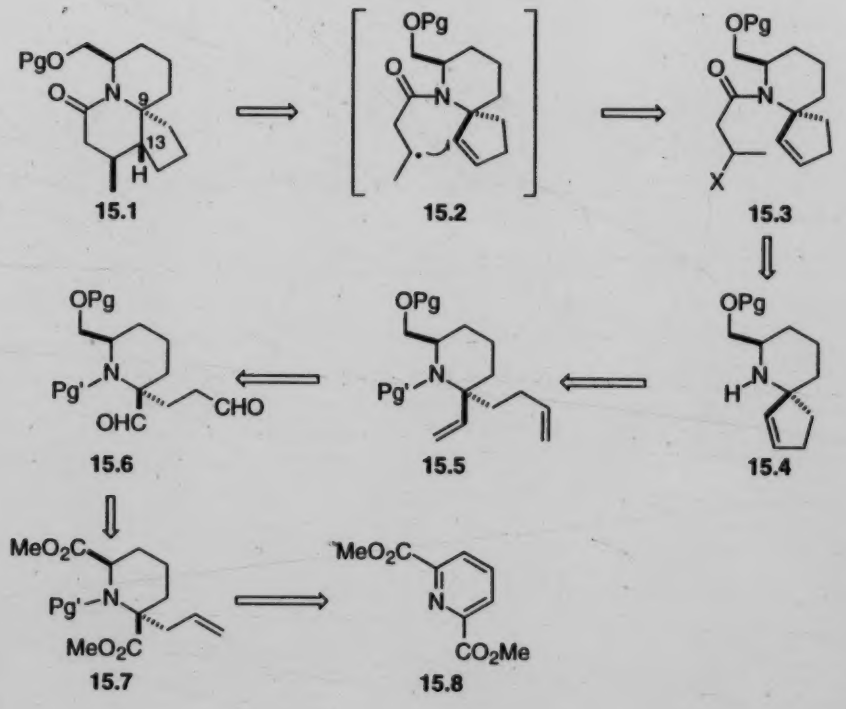
Results and discussion

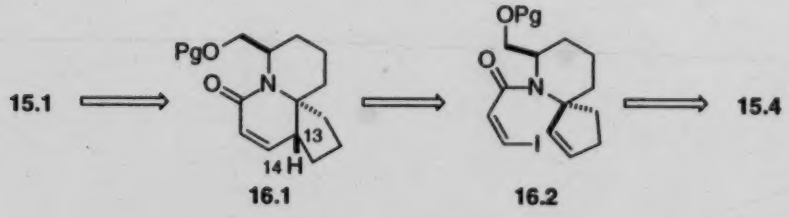
As mentioned in the previous section, construction of the functionalized azaspirobicyclic core of halichlorine is the main challenge in its total synthesis. Although a synthetic route[1] to this core has been established in our laboratory, a new and more efficient route is being attempted. In contrast with the earlier route, the quaternary center in the azaspirobicyclic core will be established at an early stage. The new strategy is based on the retrosynthetic analysis shown in Scheme 15.

Scheme 15



We felt that the tricyclic lactam **15.1** could be made by cyclization of radical **15.2**, which was to be generated from spirocyclic amides **15.3** [X = I, Br, PhSe, ArOC(S)O]. Thus, the side chain at C(13) of halichlorine would be constructed from **15.4** by using nitrogen as a temporary linker. Ring closing metathesis[2] of diene **15.5** should give rise to the azaspirocyclic compound **15.4**. Elaboration of diester **15.7** is expected to generate dialdehyde **15.6**, which we planned to convert into diene **15.5** by Wittig olefination. Diester **15.7** would, in turn, be produced from pyridine **15.8** by hydrogenation and subsequent asymmetric alkylation. As shown in the Scheme, the stereochemistry of the quaternary center is set at a very early stage. In this plan, asymmetric alkylation, ring closing metathesis and radical cyclization are the key steps.

Scheme 16



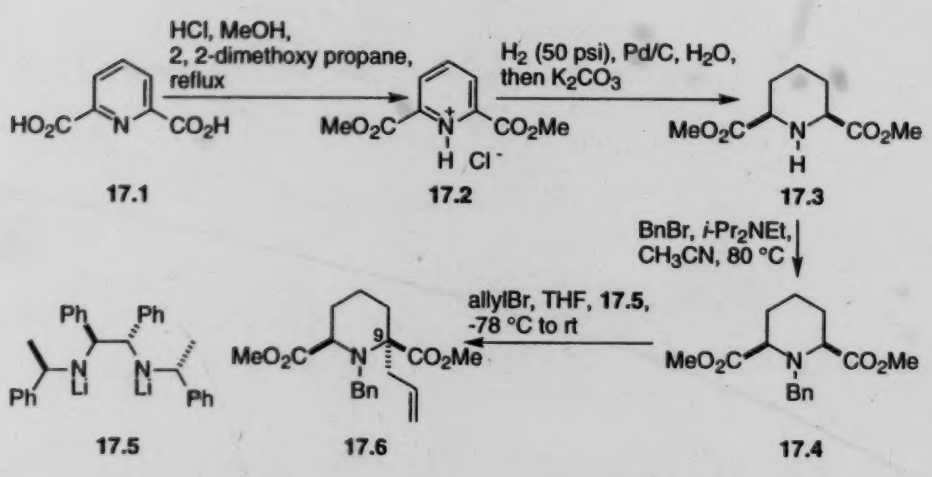
16.1 **16.2**

From the spirocyclic compound **15.4** to the tricyclic compound **15.1**, an alternative approach can also be envisioned (Scheme 16). The tricyclic compound **15.1** should be accessible from unsaturated lactam **16.1** by stereospecific methylcuprate addition from the less hindered face. The

carbon-carbon bond formation between C(13) and C(14) might be accomplished by an intramolecular Heck reaction under reductive conditions.[3] The amide **16.2** would be prepared from the spirocyclic compound **15.4**.

Before I took over this project, this synthetic plan had been studied by Mr. Vince Yeh.[4] His work is summarized in the following paragraphs.

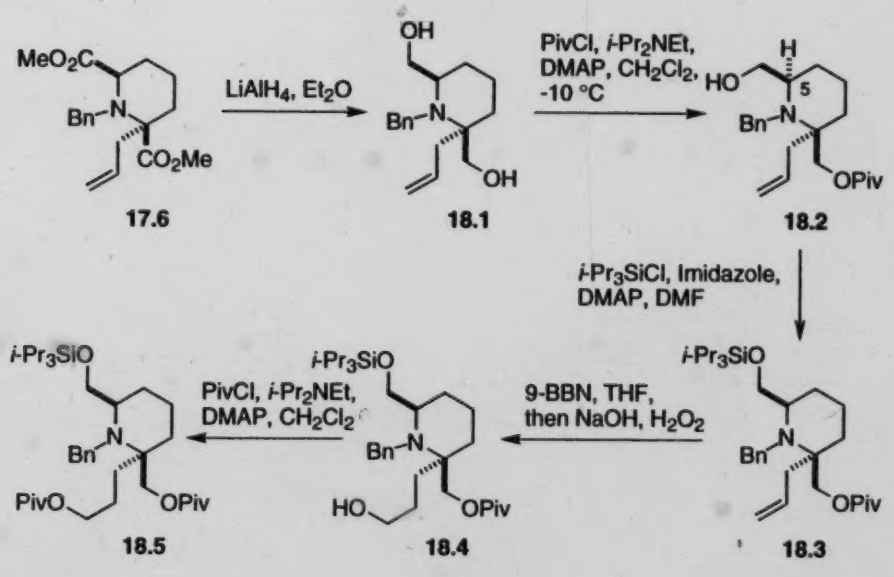
Scheme 17



The synthesis started with the readily available 2,6-pyridinedicarboxylic acid **17.1**. Esterification,[5] using 2,2-dimethoxypropane under acidic conditions, gave the hydrochloride salt **17.2**. The salt was subjected to high pressure hydrogenation and subsequent neutralization to produce the *cis*-piperidine diester **17.3** exclusively,[5] and the nitrogen was protected by benzylation with BnBr. Then asymmetric allylation, a published procedure developed by

Simpkins,[6] using the chiral dilithium amide base **17.5**,[7] served to accomplish the construction of the C(9) stereogenic center. The enantioselectivity in the alkylation reaction has not been rationalized.[6] Presumably, the chiral amide is aggregated with the enolate substrate, but the way in which this controls the stereochemical sense of alkylation is unclear.

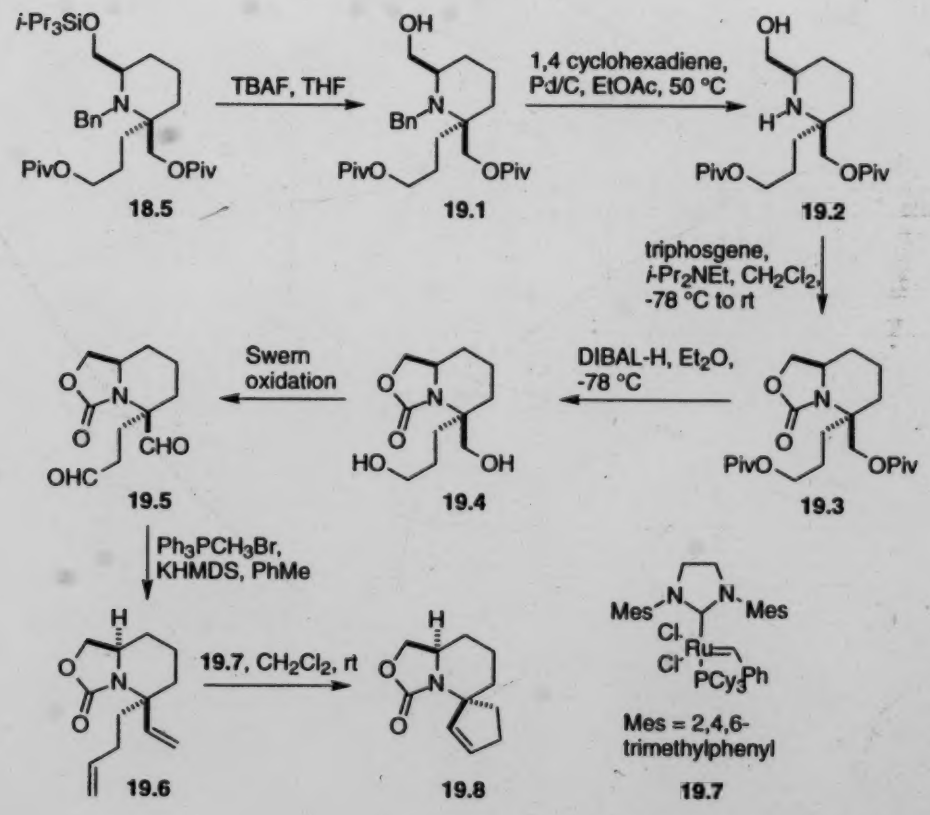
Scheme 18



Diester **17.6** was reduced to diol **18.1** by $LiAlH_4$. Selective protection of what would seem to be the more sterically hindered hydroxyl group by acylation with *t*-BuCOCl gave **18.2**. The structure of **18.2** was confirmed by extensive NMR studies including G-COSY, HMBC, HMQC, and T-ROESY measurements. In addition, the ^1H NMR signal for C(5)H remains at high field (ca δ 2.8 for **18.2**); while the

undesired compound (with the OH and OCOBu-*t* functions interchanged) which was isolated in small amounts, gives a signal at lower field (ca δ 3.1). Thus, the characteristic proton signal corresponding to C(5)H indicates which oxygen has been protected. Silylation and subsequent hydroboration-oxidation produced silyl ether **18.4**. It turned out that the benzyl protecting group of the amine nitrogen had to be changed to a carbamate or sulfonamide[8] since the amine poisoned the Grubbs' catalyst that was used later to generate

Scheme 19



a five-membered ring. Before replacing the *N*-benzyl group, the decision was made to protect the C(5) hydroxymethyl functionality in **18.4** as its pivaloyl ester, so that both oxygen functions could later be deprotected at the same time (see Scheme 19, **19.3→19.4**).

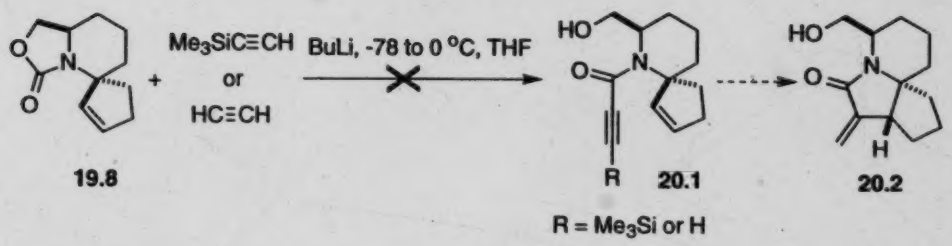
Intramolecular acylation of **19.2**, which was made from **18.5** by desilylation and hydrogenolysis, turned out to be the most efficient way to protect the sterically hindered nitrogen. Subsequent elaboration included deprotection of the pivaloyl groups to diol **19.4**, Swern oxidation to dialdehyde **19.5**,[9] and Wittig olefination to diene **19.6**. Finally, diene **19.6** was subjected to the Grubbs' catalyst[10] to afford the azaspirocyclic compound **19.8**.

This is the point at which I took over the project. As mentioned in the synthetic plan (Schemes 15 and 16), the next main step would be radical cyclization or Heck coupling, and so the immediate goal was to make the precursors for these cyclizations.

First of all, we tried to open the carbamate by using an alkynyl lithium (**19.8→20.1**) (Scheme 20) in the expectation that a subsequent 5-*exo*-trig radical cyclization, induced by stannyl radicals, would give the tricyclic compound **20.2**.

To this end, the carbamate was exposed to the action of the lithium salt of trimethylsilyl acetylene, which was generated by slow addition of BuLi at low temperature to the parent acetylene.[11] However, the desired acetylenic amide **20.1** was not found. Even when lithium acetylide itself – a

Scheme 20



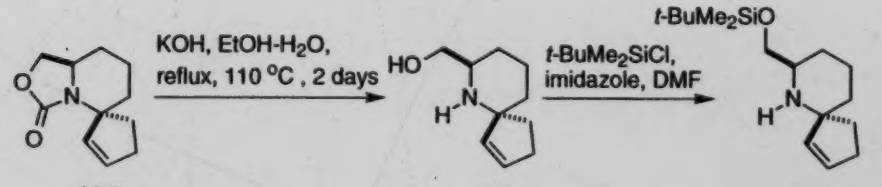
19.8 20.1 20.2

R = Me_3Si or H

smaller reagent – was tried, the starting carbamate was recovered. Because of the apparent inertness of the carbonyl group we tried to hydrolyze the carbamate first (Scheme 21), and then protect the hydroxyl group of compound **21.1** by silylation, leaving the amino group (as in **21.2**) for acylation with a suitable acid chloride.

Acylation approach

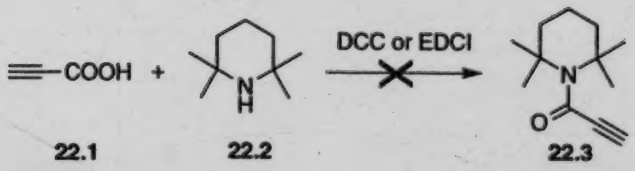
Scheme 21



19.8 21.1 21.2

The desired acetylenic amide might also be reached by condensation of the amine with propiolic acid.[12] To test this possibility we used the hindered amine 2,2,6,6-tetramethylpiperidine (**22.2**) as a model for the valuable amine **21.2** (which requires 18 steps for its synthesis).

Scheme 22

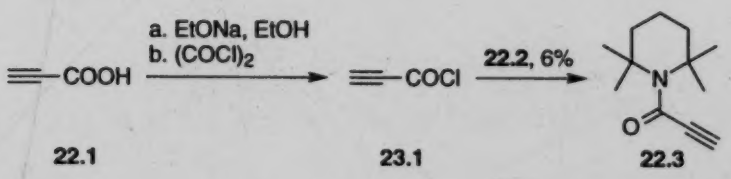


22.1 **22.2** **22.3**

EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

However, attempted condensation (Scheme 22), using DCC or EDCI [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride] failed to give amide **22.3**. We then tried acylation with propynoyl chloride. This was made from

Scheme 23

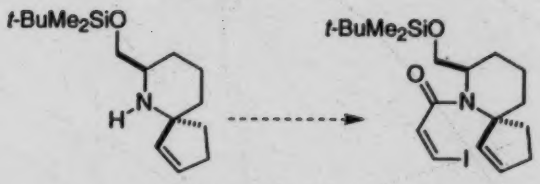


22.1 **23.1** **22.3**

the corresponding acid in two steps by treatment with EtONa[13] to form the sodium salt, and then with $(COCl)_2$. The crude product was used to acylate the model amine **22.2**. However, the desired amide **22.3** was formed in only 6% yield. If the ammonium salt[14] of propiolic acid was used instead of the sodium salt, the amide was formed in 20% yield.

At this stage we decided to try to make a precursor (**16.2'**, see Schemes 16 and 24) for Heck coupling.

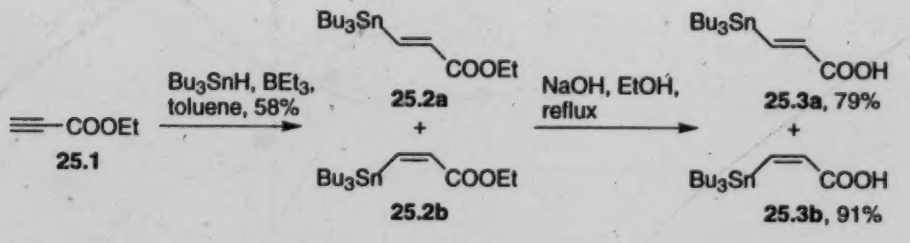
Scheme 24



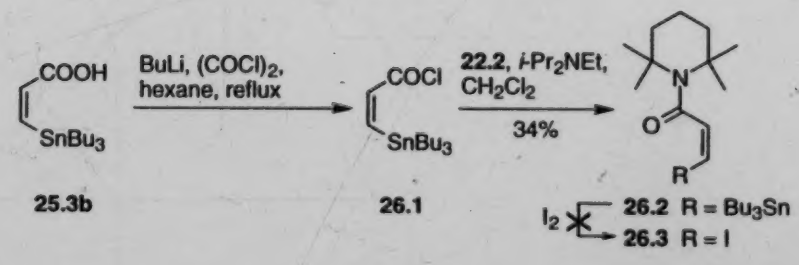
21.2 **16.2'**

We started with ethyl propiolate **25.1**. Pure *Z*- and *E*-tributyltin acrylates **25.2a** and **25.2b** were generated in a 1:1 ratio by Et_3B-mediated radical addition.[15] Acids **25.3a** and **25.3b** were then formed individually by hydrolysis, using NaOH in refluxing EtOH. We used **25.3b** for the following experiments.

Scheme 25

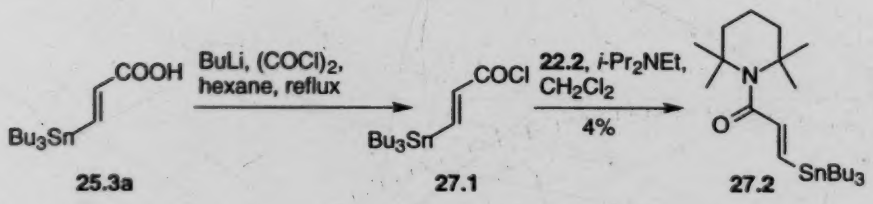


Scheme 26



Acid chloride **26.1** was made by chlorination of the lithium salt, generated *in situ* from the corresponding acid and BuLi. The resulting reaction mixture was then added to a solution of tetramethylpiperidine (**22.2**) and *i*-Pr_2NEt in CH_2Cl_2. Amide **26.2** was obtained in 34% yield. Unfortunately, an attempt to replace the Bu_3Sn group by I, using I_2 in CH_2Cl_2, failed; the starting material was destroyed, and a complex mixture was obtained.

Scheme 27

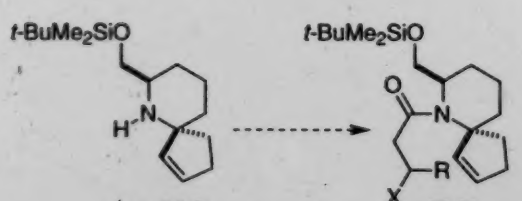


25.3a **27.1** **27.2**

We also tested the *E*-isomer **25.3a**, but an even lower yield of acylation product was obtained (ca 4%).

Next, we tried to convert **21.2** into a precursor (**15.3'**) that would be suitable for radical cyclization (see Schemes

Scheme 28

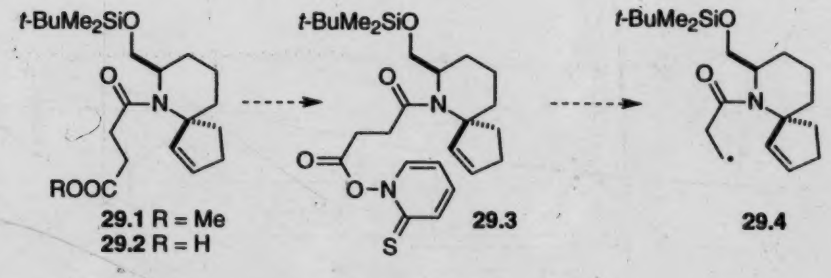


21.2 **15.3'**

R = H or Me

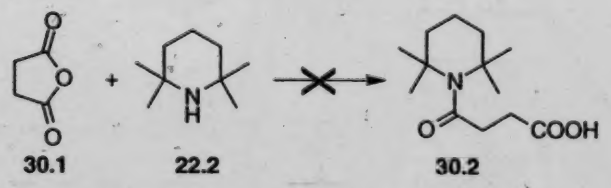
15 and 28). We planned to do this by acylation so as to obtain an ester **29.1** or an acid **29.2**. Further elaboration would then give the radical precursor **29.3**, and this would provide the radical species **29.4**.

Scheme 29



We wanted to try first succinic anhydride (**30.1**) as the acylating agent to form **30.2**. Again we tested the reaction by using the model compound **22.2**. However, the desired acid was not formed, even under forcing conditions (i.e., prolonged stirring and refluxing in PhMe).

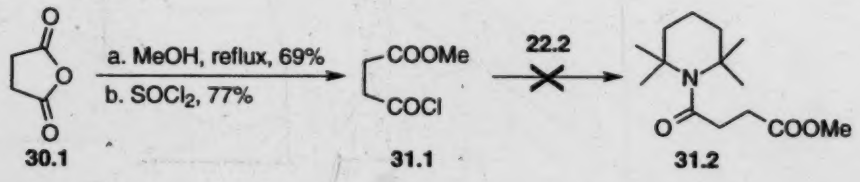
Scheme 30



Clearly, a more reactive agent such as an acid chloride was needed for the acylation. Succinic anhydride was

monoesterified by refluxing in MeOH, and the resulting carbomethoxy acid was heated in $SOCl_2$.[16] The pure acid chloride **31.1** was obtained in 77% yield by vacuum distillation. However, acylation of our test hindered amine to give **31.2** was not successful, using Et_3N/DMAP, K_2CO_3 or *i*-Pr_2NEt as the base.

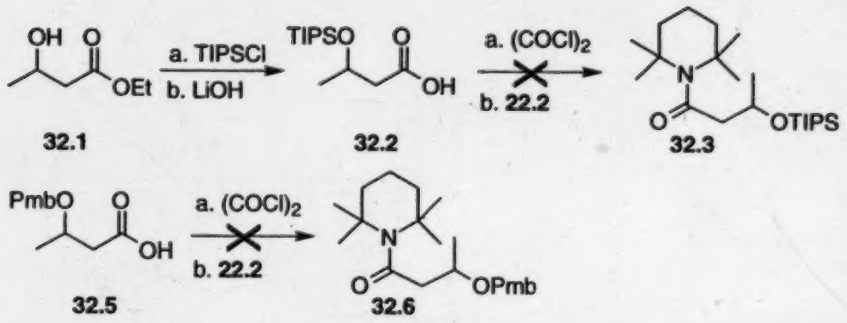
Scheme 31



We then turned our attention to compounds of type **15.3**. To this end, the hydroxyl group in the 3-hydroxybutyrate **32.1** was protected as a silyl ether. Hydrolysis gave acid **32.2**, and treatment[17] with $(COCl)_2$ then gave the desired acid chloride. However, acylation did not produce the expected amide **32.3**. When the same sequence was repeated using *p*-methoxybenzyl (Pmb) instead of silyl protection for the hydroxyl group, the acylation was again unsuccessful, and the Pmb group was lost during the experiment. We surmised that tetramethylpiperidine is simply too hindered, and so we tried compound **21.2** itself in the acylation, using the acid chloride derived from **32.5**, but here, too, we were unsuccessful, and obtained only a complex mixture.

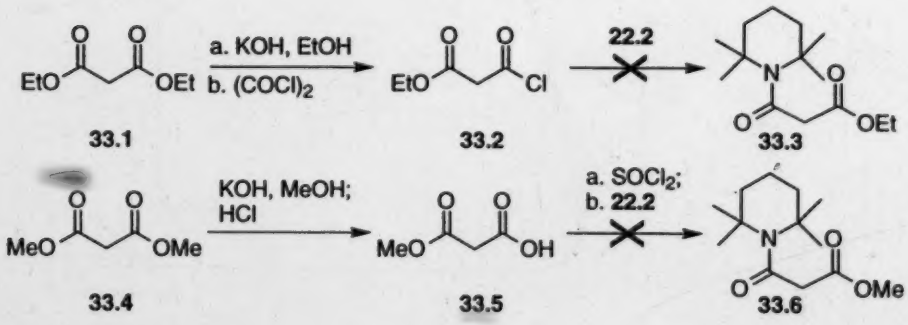
The large size of the silyl or Pmb protecting groups might prevent the acid chloride from attacking the hindered

Scheme 32



amine, and so we tried to use malonate derivatives which could later be elaborated into radical precursors of type **15.3**.

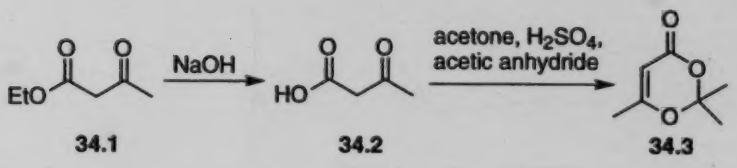
Scheme 33



Diethyl malonate (**33.1**) was hydrolyzed, and the resulting potassium salt was subjected to treatment with $(COCl)_2$[18] to produce the monoethyl malonic chloride **33.2**. However, attempted acylation of **22.2** did not give the desired product. Using dimethyl malonate (**33.4**), hydrolysis,[19a] chlorination[19b] and attempted acylation also met with failure.

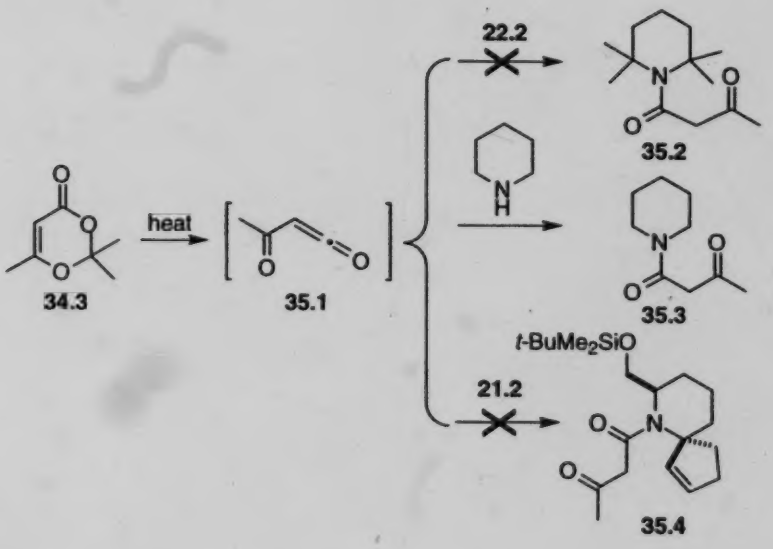
We now decided to use a ketene, which is a very reactive type of acylating agent. The appropriate ketene precursor was **34.3**, and it was made in two steps[20] from ethyl acetoacetate (**34.1**), as shown in Scheme 34.

Scheme 34



With the diketene acetone adduct **34.3** in hand, acylation of tetramethylpiperidine **22.2** with ketene **35.1**, generated *in situ* by heating[21] (refluxing xylene), gave none of the desired

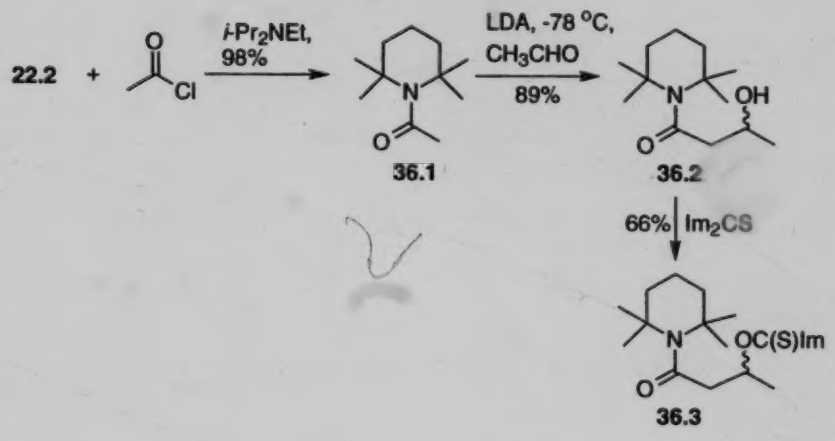
Scheme 35



amide **35.2**. In order to test this procedure, we tried piperidine as the acylation substrate. To our delight, the desired amide **35.3** was obtained in nearly quantitative yield. However, when this ketene was applied to compound **21.2** – the intermediate in our actual synthetic scheme – the acylation failed.

These unsuccessful attempts indicated that the nitrogen in compound **21.2** is too hindered to be approached by the relatively large acylating agents we had used. We realized that acetyl chloride is the smallest acylating agent we could use for our synthesis, and so we investigated this reagent.

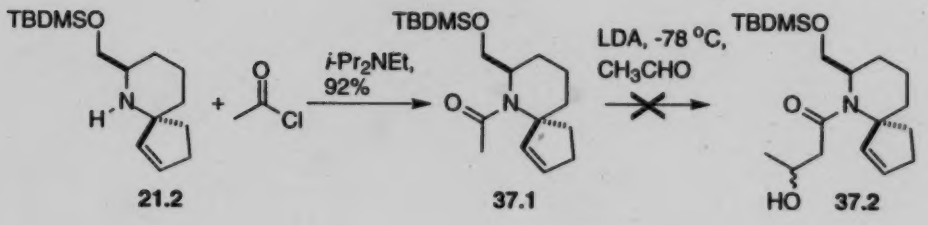
Scheme 36



We started with the model compound **22.2** again. Acylation with AcCl, using *i*-Pr_2NEt as the base, gave amide **36.1** in high yield. This was a very pleasing observation. In the following steps we extended the side arm (**36.1→36.2**)

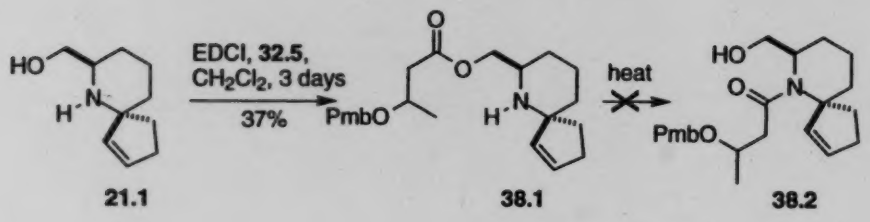
by aldol condensation[22] and modified the hydroxyl group so that it would generate the radical species. After examining several reagents,[23] thiocarbonyldiimidazole turned out to be the best reagent for attachment of a thiocarbonyl unit (**36.2→36.3**). These reactions worked well, except that the reactions (**36.1→36.2** and **36.2→36.3**) did not go to completion. Although this sequence was not perfect, it was still worthy of being applied to the real compound of interest (**21.2**).

Scheme 37



Indeed, the acylation of **21.2** with AcCl gave an exciting result, since the desired product was formed in excellent yield on using Hünig's base, but not Et_3N. However, to our disappointment, the next step – aldol condensation – did not succeed, and only starting material was recovered. Even when additives such as DMPU,[24a] LiBr,[24b] $TiCl_4$,[24c] or Bu_2BOTf[24d] were added to assist the aldol condensation, no improvement was achieved. We surmised that the large silyl protecting group in **37.1** might somehow disfavor the aldol condensation, and so we desilylated **37.1**, but even then the aldol

Scheme 38



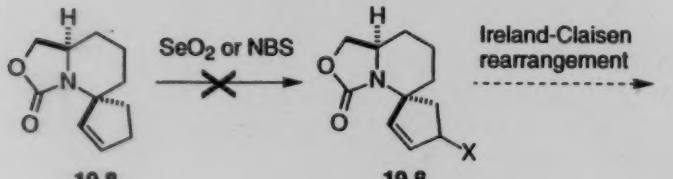
21.1 **38.1** **38.2**

condensation (not shown) with a two-fold excess of LDA did not give the desired product, and only the starting material was recovered.

We attempted intramolecular acyl transfer (**38.1**→ **38.2**). However, as shown in Scheme 38, the acyl transfer did not occur even on heating in 1,2-dichlorobenzene (160 °C) for 5 h.

If the allylic position in **19.8** were to be oxidized, the subsequent elaboration via Ireland-Claisen rearrangement would complete the carbon-carbon bond formation between C(13) and C(14) of halichlorine. However, when the tricyclic compound **19.8** was subjected to treatment with SeO_2 or NBS, only starting material was recovered.

Scheme 39



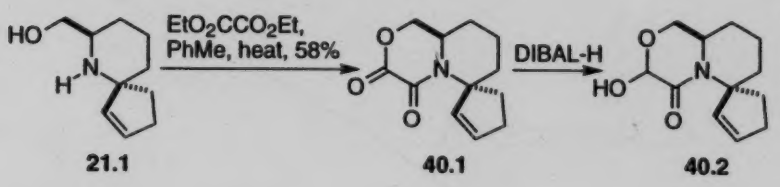
19.8 **19.8**
X = Br or OH

As mentioned before (see Scheme 20), the carbonyl carbon in tricyclic compound **19.8** is not very reactive, and, in order to improve the reactivity, we prepared a related compound (**40.1**), in which the carbonyl carbon of the lactone functionality was expected to be much more reactive.

Lactone approach

Compound **40.1** was made from **21.1** by a modified literature procedure that had been reported for a totally different substrate.[25] The desired lactone **40.1** was obtained in 58% as a white solid.

Scheme 40

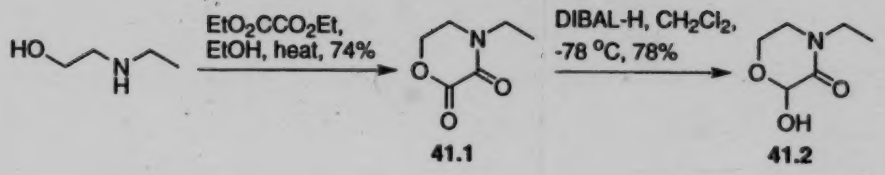


21.1 **40.1** **40.2**

Selective reduction with DIBAL-H would be expected give lactol **40.2**, which would be opened by appropriate nucleophiles to generate the radical precursor of type **15.3**. Again, we made a model compound (**41.1**) on which to practice the proposed reactions. The model was made from ethylamino-ethanol by heating with EtO_2CCO_2Et.[25] Selective reduction with DIBAL-H at a low temperature gave lactol **41.2** in 78% yield.

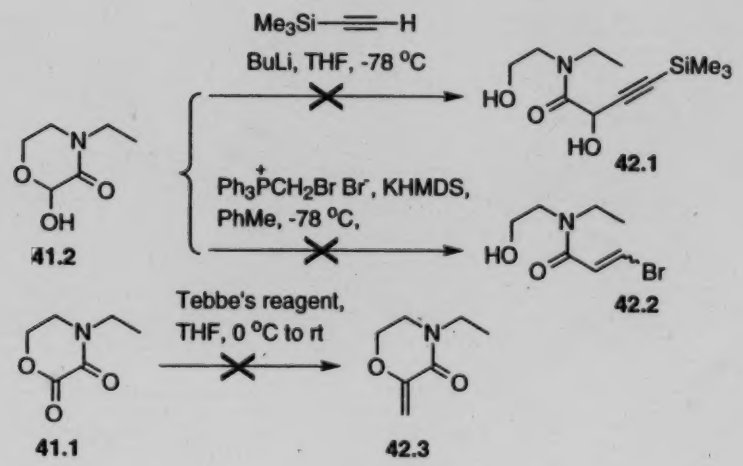
We assumed that this lactol would be opened easily by nucleophilic attack but, as shown in Scheme 42, all attempts

Scheme 41



to this end failed. Lactol **41.2** was first subjected to the action of lithium trimethylsilylacetylide,[26] generated *in situ* from trimethylsilylacetylene and BuLi. None of the desired diol **42.1** was found, but the starting material was destroyed. Even when anhydrous $CeCl_3$ was added to assist the nucleophilic addition, no improvement was achieved.

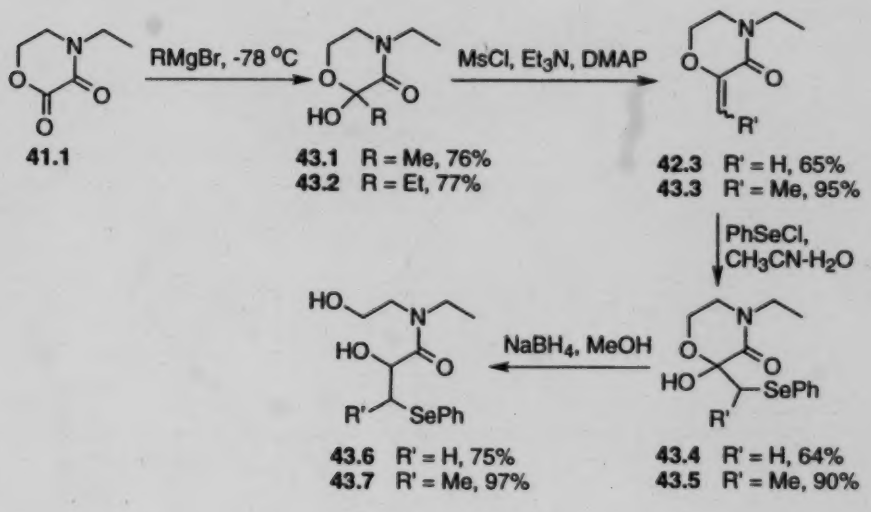
Scheme 42



We next tried a Wittig reagent. Again, no desired olefin **42.2** was produced. Even the use of different bases (NaHMDS and *t*-BuOK[27]) or different reaction temperatures (-78

°C, 0 °C and room temperature) gave only either starting material or complex mixtures. We also tried direct olefination of **41.1** by using Tebbe's reagent. If we could form olefin **42.3**, subsequent elaboration would give a lactol, which might be opened by reduction (see Scheme 43). However reaction with the Tebbe reagent met with failure as well, and a complex mixture was formed.

Scheme 43



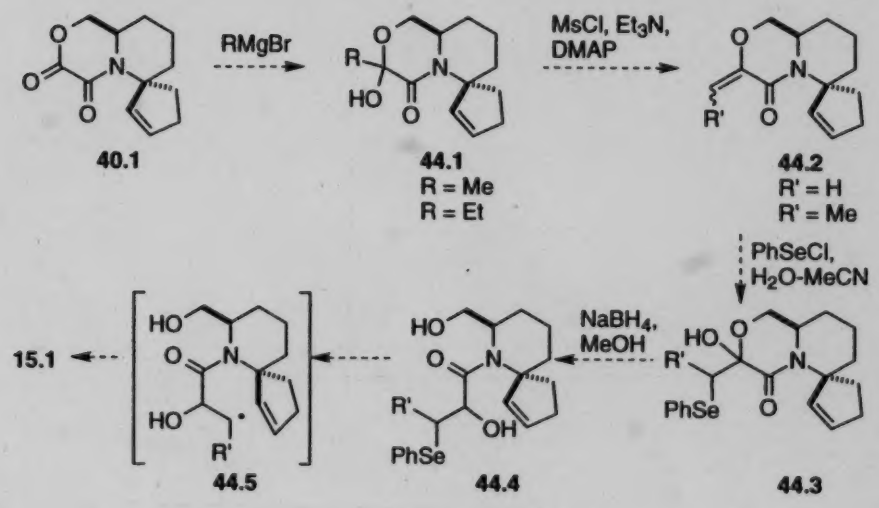
We then found that we could use another route to make olefin **42.3**. This route involved a Grignard addition-dehydration sequence. Lactone **41.1** was subjected to the action of MeMgBr at -78 °C to generate lactol **43.1** in 76% yield. Dehydration with $MeSO_2Cl$ under basic conditions gave the desired olefin **42.3** in 65% yield, and 26% of the starting material (**43.1**) was recovered. Then we attached a

phenylselenyl group in order to be able to generate a radical species. The phenylselenyl substituted lactol **43.4** was obtained in 64% yield by using PhSeCl in a 5:1 mixture of MeCN and water.[28] Reductive ring opening by $NaBH_4$ in MeOH then gave **43.6**.

When one examines the structure of halichlorine, it is seen that there is a methyl group at C(14), and we recognized that if we could install this methyl group early, the synthetic plan would definitely be simplified. Thus, we used EtMgBr instead of MeMgBr for the nucleophilic addition (**41.1→43.2**). With this starting lactol (**43.2**), the subsequent reactions (**43.2→43.3→43.5→43.7**) under the same conditions used for the methyl lactol **43.1**, worked much better.

Having these promising results in hand, we were now

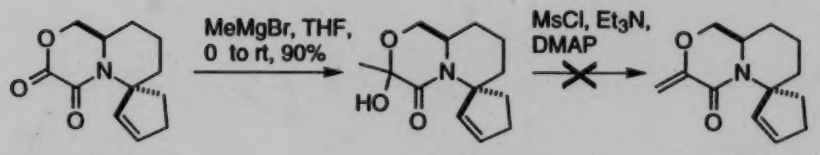
Scheme 44



ready to try the ideas on the actual halichlorine route, and so we planned to subject lactone **40.1** to the four-step sequence in order to generate the radical precursor **44.4**. Under radical conditions, we hoped that the desired tricyclic lactam (of type **15.1**) would be produced by cyclization of radical species **44.5**.

However, when this four-step sequence was put to the test, the reactions did not work as smoothly as expected.

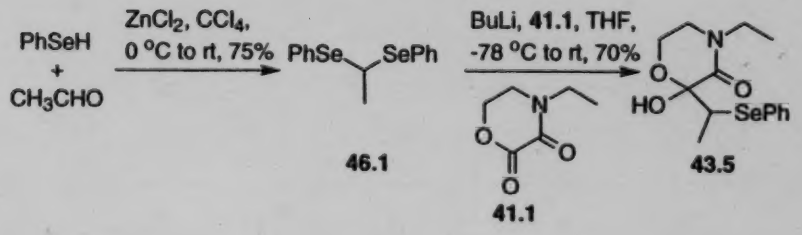
Scheme 45



40.1 **45.1** **45.2**

Grignard addition to lactone **40.1** gave lactol **45.1** in high yield. However, dehydration under the previous successful conditions gave a complex mixture. After further consideration, we found that we could solve this problem by using the phenylselenide derivative **46.1**. Actually, we had

Scheme 46

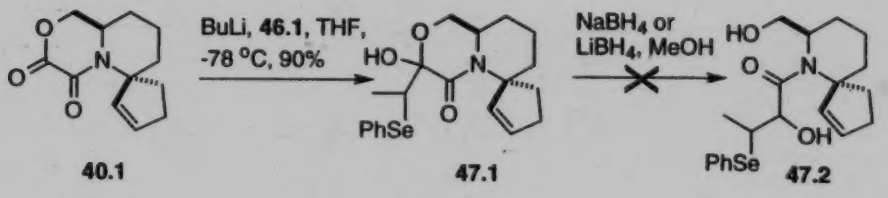


46.1 **41.1** **43.5**

also realized that selective reaction of the enol ether double bond in **44.2** to make **44.3**, which is a key step in the synthetic plan (Scheme 44), might be risky. The phenylselenide derivative **46.1** avoids this risk, and we could save two steps en route to the radical precursor **44.4**.

The phenylselenide derivative **46.1** was made by the literature procedure[29] from PhSeH and MeCHO in the presence of $ZnCl_2$. The reaction of the model compound **41.1** with the phenylselenyl carbanion, generated *in situ* from **46.1** with BuLi,[30] gave **43.5** (70% yield), identical to material obtained previously.

Scheme 47

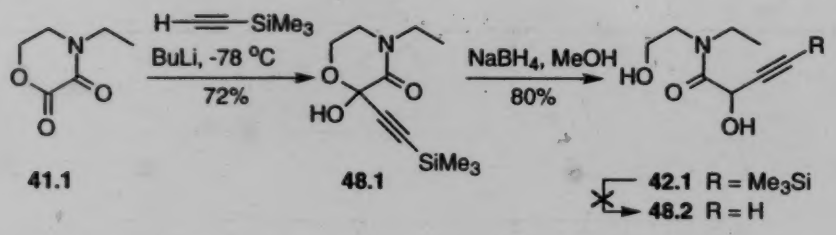


We now tested the phenylselenide agent on the halichlorine system with confidence. Indeed, nucleophilic addition to the lactone carbonyl gave the desired product **47.1** (as a mixture of four isomers) in excellent yield, and so only one more step (reductive opening of the lactol) was required to reach the radical precursor **47.2**. Unfortunately, this reductive cleavage, using $NaBH_4$ or $LiBH_4$ in MeOH, did not give the expected diol **47.2**; only starting lactol or its epimerized isomer was recovered. No improvement was obtained on extending the reaction time or on adding $CeCl_3 \cdot 7H_2O$.

DIBAL-H was also tried for this reductive cleavage. When 1 equiv. of DIBAL-H was used at -78 °C, the starting lactol was recovered; while with 3 equiv. of DIBAL-H or when the reaction mixture was warmed to room temperature, a complex mixture was formed.

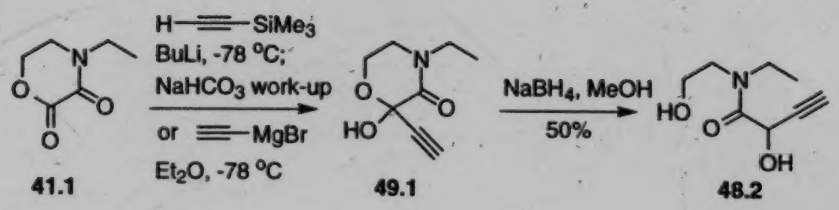
We continued to test this lactone approach by using different nucleophiles. We hoped that lithium trimethylsilylacetylide would give a better result.

Scheme 48



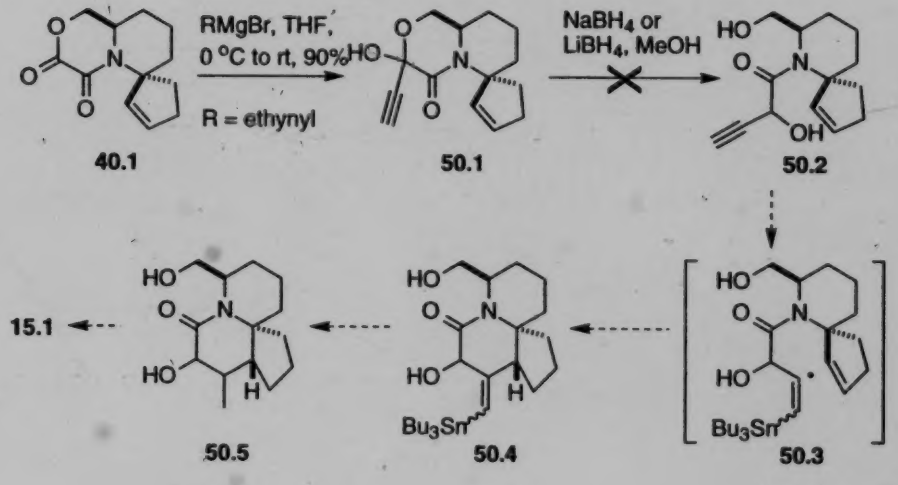
As shown in Scheme 48, the nucleophilic addition to **41.1** and the reductive cleavage[31] of **48.1** occurred nicely. Compound **42.1** was the product we had expected by using the reversed sequence shown in Scheme 42. In that earlier work, the experiments were unsuccessful. Desilylation of diol **42.1** with K_2CO_3 in MeOH or Bu_4NF gave a complex mixture, and none of the desired acetylene **48.2** was found. It would seem that this plan is thwarted by the normally simple step of deprotecting the trimethylsilyloxy function. Fortunately, we quickly realized that the silicon protecting group could be removed at an earlier stage.

Scheme 49



As expected, the desilylated product **49.1** was obtained from **41.1** (42% yield) by using $NaHCO_3$ workup conditions. Reductive cleavage of lactol **49.1** produced diol **48.2** in 50% yield. If ethynylmagnesium bromide was used as the nucleophile in the transformation of **41.1** into **49.1**, the desired lactol was obtained in 51% yield.

Scheme 50



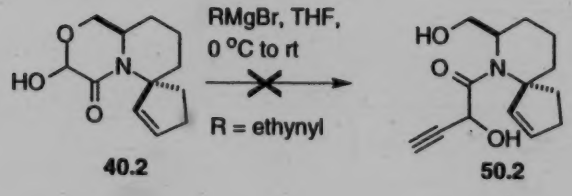
With these results as background, we applied the acetylenic Grignard reagent to the actual compound of

interest. We intended that the radical cyclization would occur through intermediate **50.3** (which is a radical species of type **15.2**), obtained from acetylene **50.2**. The radical cyclization would give lactam **50.4**, and subsequent elaboration would afford a tricyclic lactam in our route to the azaspiro core of halichlorine.

Nucleophilic addition to lactone **40.1** gave **50.1** in excellent yield. However, the subsequent reductive ring cleavage with $NaBH_4$ or $LiBH_4$ met the same failure as before, and starting material was recovered in these attempts. When the $NaBH_4$ reaction mixture was warmed to 50 °C, starting material was consumed, and a small amount (30%) of lactol **40.2** was obtained. The mechanism for formation of lactol **40.2** from **50.1** is not clear.

We then tried direct nucleophilic addition to this lactol (**40.2**), even though we were unsuccessful in this type of reaction with the model compound (see Scheme 42). As indicated in Scheme 51, no diol **50.2** was obtained.

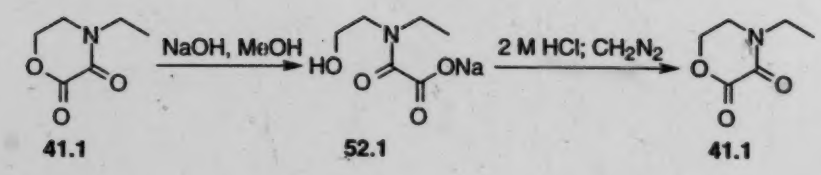
Scheme 51



40.2 **50.2**

As the major problem was the ring opening, we wondered if we could hydrolyze the lactone and then protect the

Scheme 52

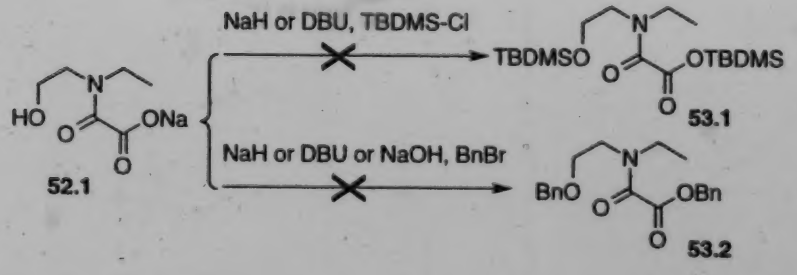


resulting hydroxyl and carboxyl functionalities by alkylation or silylation.

We examined this idea first with the model compound **41.1**. After trying several hydrolysis conditions (KOH-MeONa-MeOH,[32] LiOH·H_2O-MeOH, or NaOH-MeOH), we found that NaOH in MeOH worked best. The carboxylic acid was formed after its corresponding salt **52.1** was acidified. However, the acid was very unstable. It spontaneously reformed the lactone **41.1** even during normal evaporation of its solutions under water-pump vacuum. We avoided isolating the acid, and instead methylated it directly by using diazomethane; however, only lactone **41.1** was isolated as the final product.

We also tried direct silylation of the anhydrous

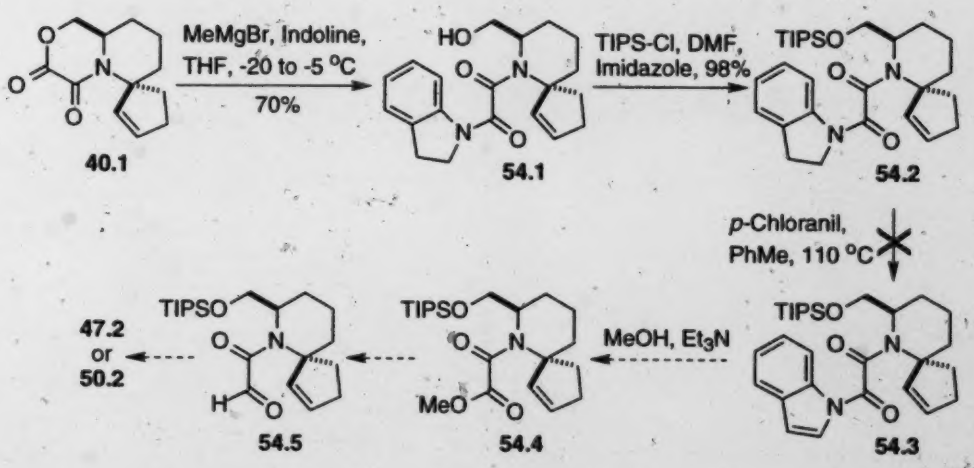
Scheme 53



carboxylic acid salt **52.1** by using DBU[33] or NaH as the base. However, the desired hydroxyl and carboxyl silyl-protected product **53.1** was not obtained, and lactone **41.1** was again the isolated product. We also tried benzylation of the carboxylic acid salt **52.1** by using NaH or DBU or NaOH as the base. A complex mixture was obtained, and none of the desired benzyl-protected product **53.2** was found.

In order to open lactone **40.1**, we tried to form amide **54.1**. Our intention was that the resulting hydroxyl group would be protected (**54.1→54.2**), and the protecting indolinyl functionality would be oxidized[34] to an indolyl group (**54.2→54.3**). This is a good leaving group and we expected that it would easily be replaced by a methoxy group (**54.3→54.4**). DIBAL-H reduction would then give aldehyde **54.5**, which would react with nucleophiles to give products **47.2** or **50.2** (see Schemes 47 and 50) – the desired radical

Scheme 54



precursors.

Lactone **40.1** was opened with indoline by using MeMgBr as the base,[35] and amide **54.1** was obtained in 70% yield. Silylation gave the indoline derivative **54.2** in 98% yield. However, oxidation of **54.2** with *p*-chloranil[34] gave only a complex mixture; hence the subsequent steps could not be tried.

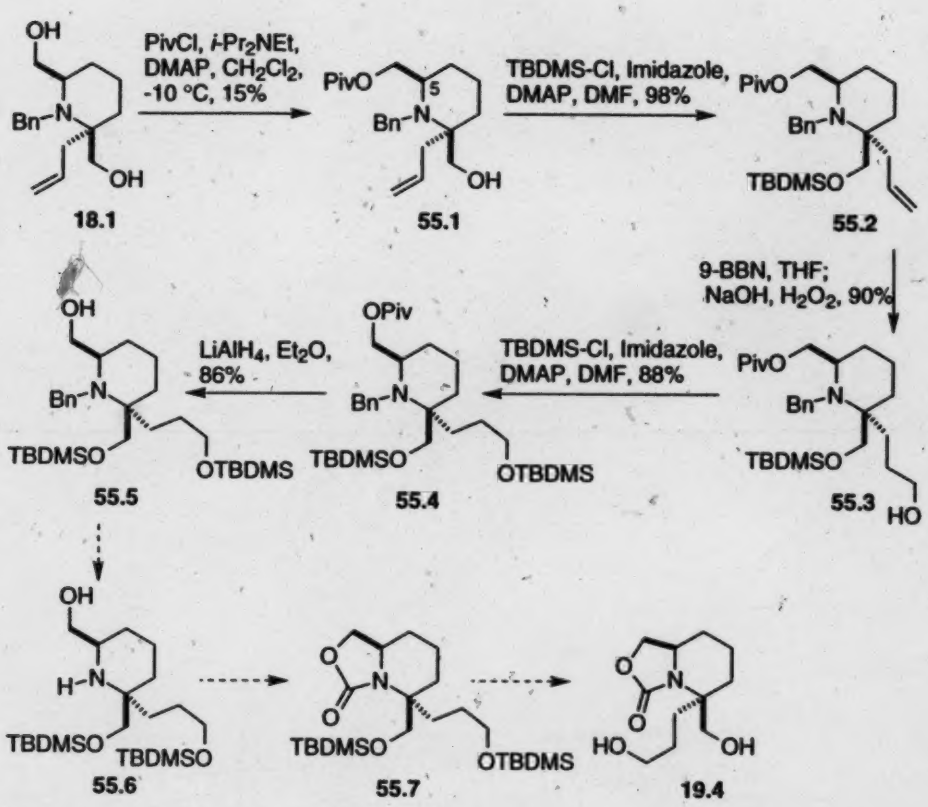
I have discussed all the attempts we had made to approach the Heck coupling precursor or radical cyclization precursor. Unfortunately, we failed in all of these attempts, and so we now decided to modify the synthetic route to the azaspiro core of halichlorine.

Before I discuss the new route, I should deal with some other results obtained when we were pursuing the old synthetic plan.

We found that while we were scaling up the preparation of the starting material, we obtained several grams of byproduct **55.1** in the conversion of **18.1** to **18.2**. We thought we could recycle this byproduct by a 7-step sequence to reach compound **19.4** (Scheme 19), which had previously been made from **18.2** (see Scheme 18).

Silylation (**55.1**→**55.2**), 9-BBN hydroboration (**55.2**→**55.3**), silylation again (**55.3**→**55.4**) and reductive deprotection (**55.4**→**55.5**) gave compound **55.5** without any problems and in good yields. However, hydrogenolysis of compound **55.5** failed. We did not try any other hydrogenolysis method besides 1,4-cyclohexadiene in the

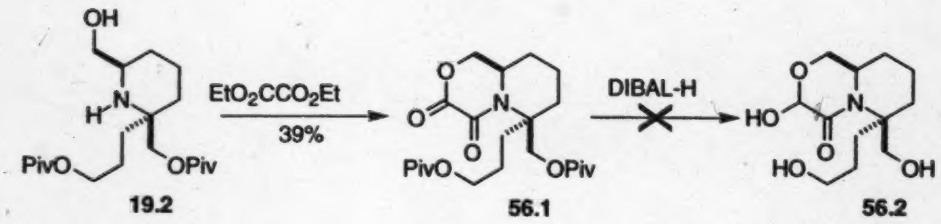
Scheme 55



presence of Pd/C, since we realized that we had spent too much time and effort on trying to recycle our byproduct. Instead, we decided to recycle byproduct **55.1** by simple reduction with $LiAlH_4$ to get back the starting diol **18.1**; this was used to carry out the synthetic plan illustrated in Schemes 18 and 19.

In addition, the lactone functionality of **40.1** had been made from carbamate **19.8** by hydrolysis and subsequent reaction with EtO_2CCO_2Et (Schemes 21, 40). We thought we might install the lactone functionality at an early stage,

Scheme 56



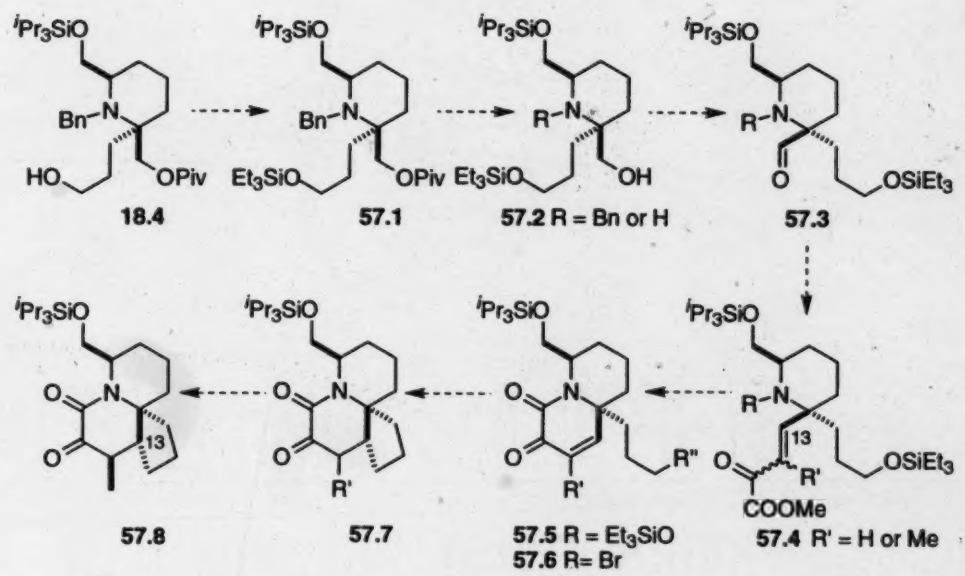
using **19.2**. Compound **56.1** was obtained in low yield by using EtO_2CCO_2Et [$(COCl)_2$ did not give the desired product]. Unfortunately, we found that the reduction of **56.1** with DIBAL-H gave a complex mixture, and none of the desired diol **56.2** was formed. Consequently, we had to follow the previous synthetic route in which lactone **40.1** was made from carbamate **19.8**.

New route to the spiro core of halichlorine

We continued to seek other synthetic routes for construction of the azaspirobicyclic core of halichlorine. After a comprehensive reanalysis, we concluded that the desired tricyclic lactam **57.7** could be made by radical cyclization from **57.6**, which, in turn, should be accessible from unsaturated ketoester **57.4** via **57.5**. Ketoester **57.4** would be made from **57.3** by Wittig or Horner-Emmons-Wadsworth olefination. Finally, aldehyde **57.3** should be easily accessible by the sequence **18.4**→**57.1**→**57.2**→**57.3**. The starting compound (**18.4**) had been prepared previously (see Scheme 18). In this synthetic plan, olefination from **57.3** to

57.4 would be best if the *Z*-isomer of **57.4** could be obtained and if the benzyl protecting group of **57.4** could removed at an early stage (i.e. R = H in **57.2**). If **57.4** is generated as the *E*-isomer, hydrogenation and subsequent double bond formation (selenoxide method) will be required.

Scheme 57

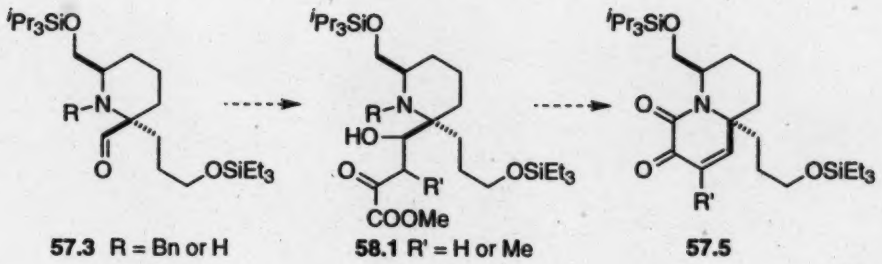


18.4 **57.1** **57.2** R = Bn or H **57.3**

57.8 **57.7** **57.5** R = Et_3SiO **57.6** R= Br **57.4** R' = H or Me

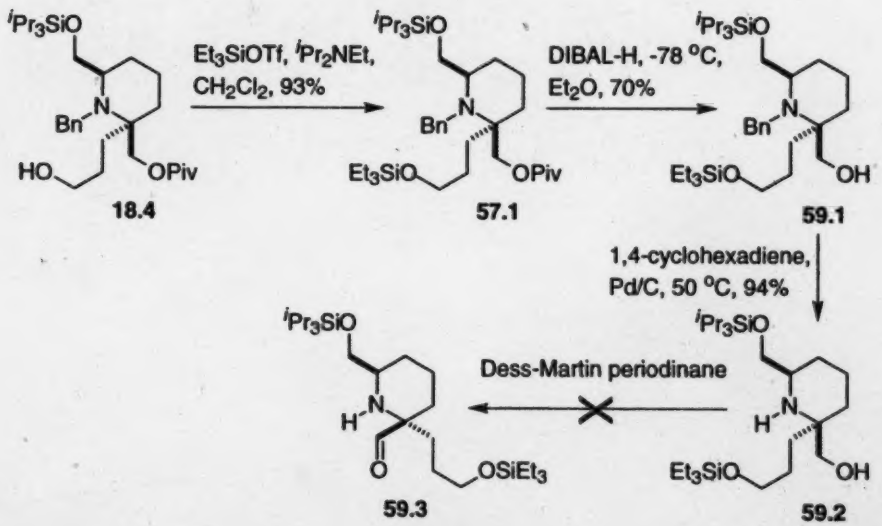
In order to avoid the problem of double bond stereochemistry, we might use aldol condensation (and subsequent dehydration) instead of olefination (Scheme 58). Unlike the synthetic routes discussed before, the side arm at C(13) of halichlorine in this strategy is put in place very early and the spirobicyclic core would be formed at a late stage.

Scheme 58



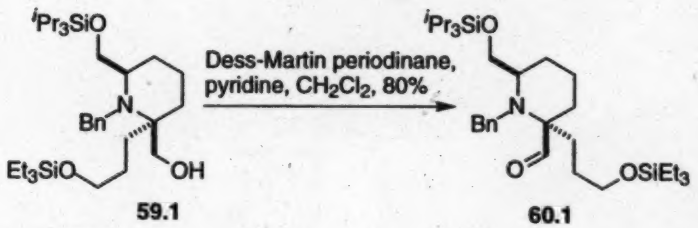
This synthetic plan was embarked on from compound **18.4**. Triethylsilyl protection gave **57.1** in 93% yield, and removal of the pivaloyl group with DIBAL-H at a low temperature generated **59.1** (70%). We attempted to effect debenzylation at this stage, and found that the desired hydroxy amine **59.2** could be made in 94% yield by using warm 1,4-cyclohexadiene in the presence of Pd/C as catalyst.

Scheme 59



An attempt to oxidize **59.2** to **59.3** by using the Dess-Martin periodinane[36a,b] was not successful, and only a complex mixture was obtained. Thus, we had to try to leave the benzyl protecting group in place until a later stage.

Scheme 60

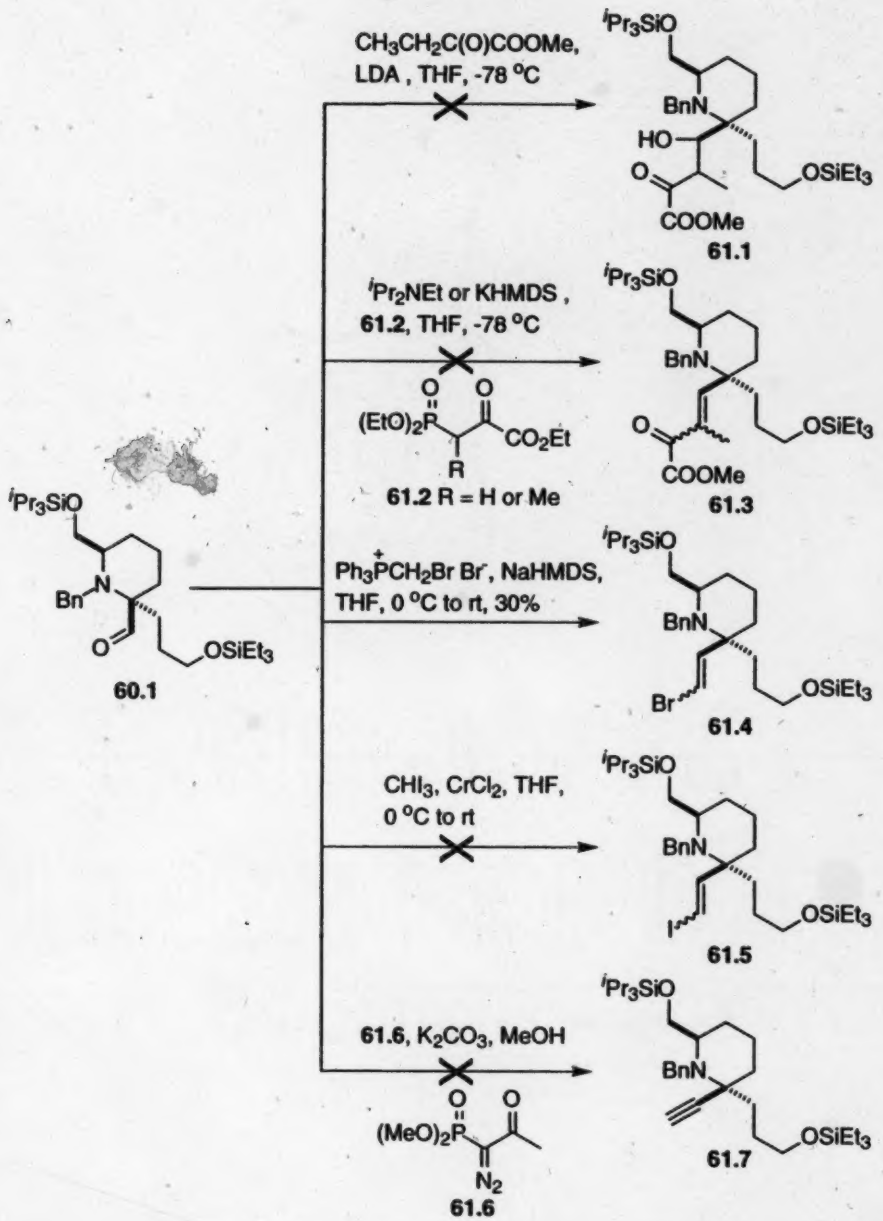


59.1 **60.1**

We tested the oxidation of compound **59.1** (with the benzyl protecting group), using the Dess-Martin periodinane. The desired aldehyde **60.1** was obtained in 80% yield. It is not clear why the amino group in **59.2** prevented[36c] the oxidation (**59.2→59.3**).

Based on the above analysis, attaching the side arm by aldol condensation, using aldehyde **60.1** would seem to be a better approach than direct olefination. However, aldol condensation with methyl 2-ketobutyrate[37] by using LDA or $(Me_3Si)_2NK$ at -78 °C did not give the desired ketoester **61.1**; only starting material **60.1** was recovered and the methyl 2-ketobutyrate was destroyed. We suspected that the ketobutyrate is too reactive and it condensed with itself. Olefination using phosphinates **61.2**[38] was equally unsuccessful. Wittig olefination gave only 30% yield of the

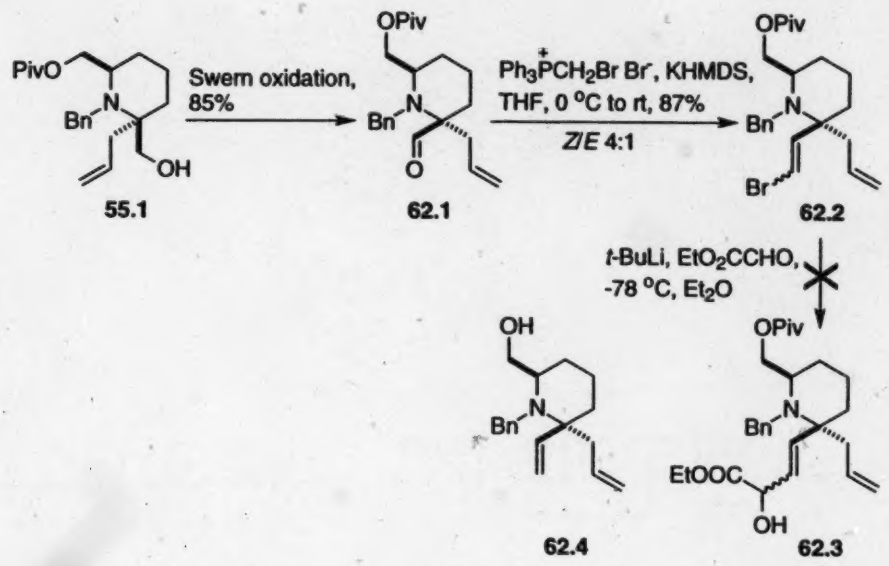
Scheme 61



desired bromoolefin **61.4**, and 60% of starting aldehyde **60.1** was recovered. Takai olefination[39] did not give the

iodoolefin **61.5**. It was reported[40] that hindered aldehydes can react with diazo compound **61.6**[41] to give acetylenes. We tried this diazo reagent on aldehyde **60.1**; however, a complex mixture was obtained, and none of the desired acetylene **61.7** was found.

Scheme 62

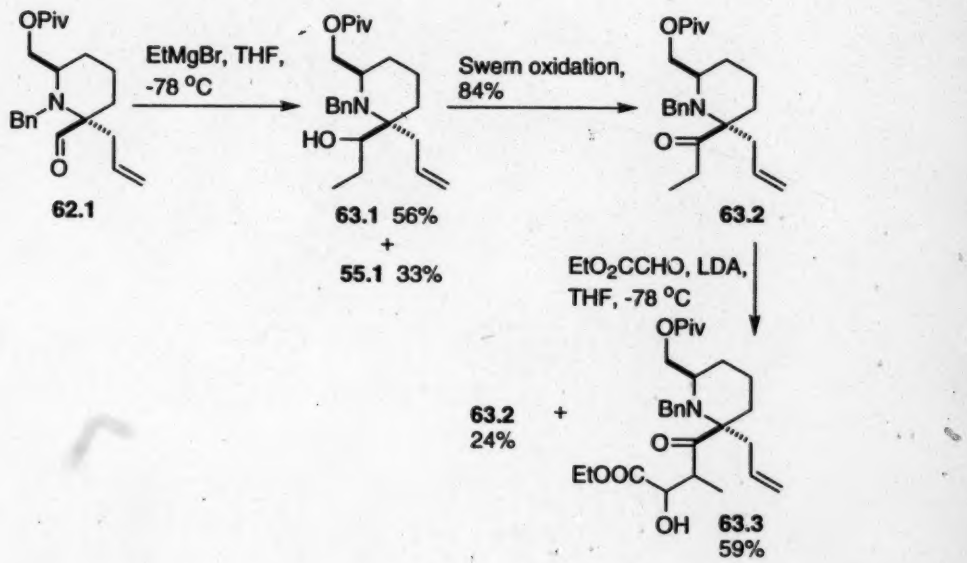


From these unsuccessful attempts, we suspected that the silyloxypropyl pendant in **60.1** hindered access to the aldehyde, and in order to avoid using this unit, we decided to elaborate the hydroxymethyl group and its derived aldehyde first, before manipulating the pendant allyl group in compound **55.1**. Swern oxidation of **55.1** gave aldehyde **62.1** in 85% yield. Indeed, Wittig olefination gave an exciting result, for **62.2** was generated in 87% yield with a *Z/E* ratio 4:1, and no starting aldehyde **62.1** was recovered. However,

extension of the brominated side arm with EtO_2CCHO, using *t*-BuLi at low temperature, gave (87%) diene **62.4**, in which the pivaloyl group had been removed. The desired product **62.3** was not found.

The success of the olefination reaction (**62.1**→**62.2**) encouraged us to try nucleophilic addition to **62.1**.

Scheme 63



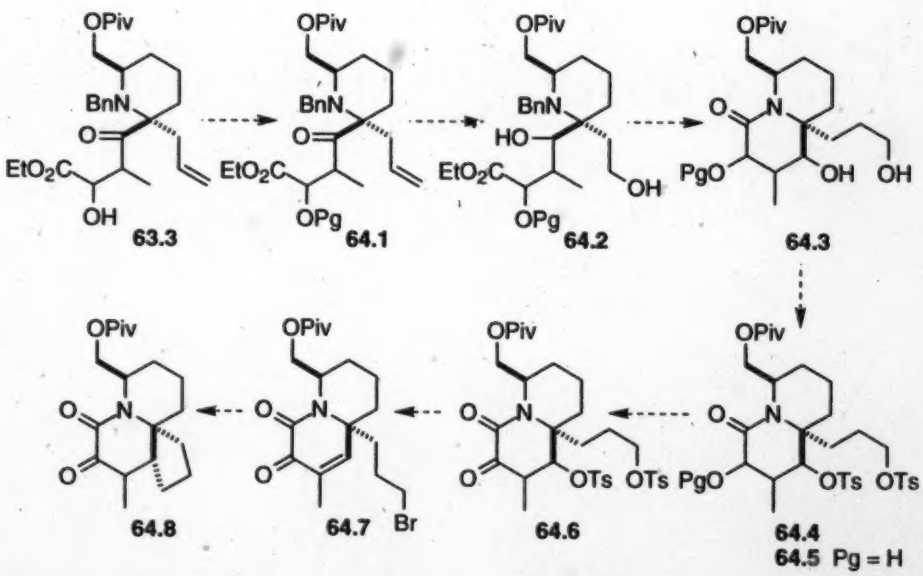
Reaction of aldehyde **62.1** with EtMgBr at -78 °C gave **63.1** in 56% yield and reduced product **55.1** in 33% yield. Ketone **63.2** was generated in 84% yield from **63.1** by Swern oxidation. Aldol condensation with EtO_2CCHO at -78 °C, using LDA, produced ester **63.3** in 59% yield, and starting material **63.2** was recovered in 24% yield. Further elaboration should lead to the azaspirobicyclic core of halichlorine.

I have brought our studies on the synthesis of halichlorine up to **63.3**. Further work on this project is continuing in our research group, and some suggestions on the subsequent steps toward halichlorine will be discussed in the following section.

Proposals to complete the synthesis of azaspiro core

Protection of the hydroxyl group in **63.3** as a benzyl or silyl ether will give ketone **64.1**. Hydroboration-oxidation of the double bond and simultaneous reduction of the ketone should then afford diol **64.2**, and hydrogenolysis and lactam formation will produce lactam **64.3**. Ditosylation and deprotection should bring the work to **64.5**, and ketolactam **64.6** will then be generated by oxidation. Dehydration and

Scheme 64



tosylate displacement with bromide should give the radical precursor **64.7**. Radical cyclization will then afford the tricyclic lactam **64.8**. The stereochemistry of the methyl group at C(14) will be epimerized if necessary.

With azaspirotricyclic lactam **64.8** in hand, further investigation will be required for the other aspects of the synthesis of halichlorine.

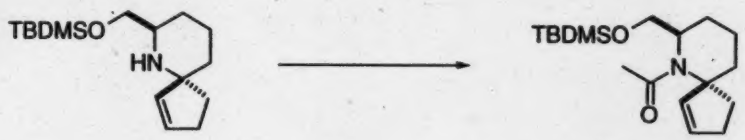
Conclusion

Several synthetic plans: an acylation approach, a lactone approach and the new route to the azaspiro core of halichlorine have been explored. Many attempts to make the radical precursor **15.3** were tested, but, unfortunately, none was successful. It appears that the nitrogen of our intermediates is extremely hindered. We then decided to modify the synthetic route in such a way that the radical precursor **57.6** would be more readily accessible. In this route, acylation of the nitrogen now involves an intramolecular process, and we expect that the reaction will now be easy. I have brought this new route up to the stage of compound **63.3**. Further elaboration should give rise to the desired azaspiro core of halichlorine.

Experimental Section

General Procedures. Unless stated to the contrary, the general experimental procedures used for the work described in the first part of this thesis were followed. In some ^{13}C NMR spectra there is signal overlap.

(5*R*,7*R*)-1-[7-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-6-azaspiro[4,5]dec-1-en-6-yl]ethanone (37.1).



21.2 **37.1**

AcCl (0.03 mL, 0.42 mmol) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of **21.2** (made by the reported method[4]) (76 mg, 0.27 mmol) and *i*-Pr_2NEt (0.10 mL, 0.57 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 30 min at 0 °C, and saturated aqueous NH_4Cl (2 mL) was then added. The ice bath was removed, stirring was continued for 30 min, and the mixture was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 10% EtOAc-hexane, gave **37.1** (80 mg, 92%) as a colorless oil: ^1H NMR ($CDCl_3$, 360 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.42-1.52 (m, 1 H),

1.60-1.80 (m, 4 H), 1.92-2.40 (m, 7 H), 2.56-2.70 (m, 1 H), 3.56-3.72 (m 2 H), 4.02-4.16 (m, 1 H), 5.44-5.52 (m, 1 H), 5.64-5.74 (m, 1 H).

(5*R*,7*R*)-[6-Azaspiro[4,5]dec-1-en-7-yl]methyl 3-[(4-Methoxyphenyl)methoxy]butanoate (38.1).

21.1 **38.1**

3-(4-Methoxybenzyloxy)butyric acid (37 mg, 0.17 mmol) in CH_2Cl_2 (2 mL plus 1 mL as a rinse) was added over 5 min to a stirred solution of **21.1** (made by the reported method[4]) (28 mg, 0.17 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (32 mg, 0.17 mmol) and Et_3N (0.04 mL, 0.29 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3 days. The reaction was monitored by TLC, and when the starting material was completely consumed, ice-water (5 mL) was added. The mixture was extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic extracts were washed successively with 5% hydrochloric acid, 5% aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using EtOAc, gave **38.1** (23 mg, 37%) as a colorless oil, which was a mixture of diastereoisomers: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.80 (m, 11

H), 1.90-2.02 (m, 1 H), 2.22-2.42 (m, 3 H), 2.58-2.62 (m, 1 H), 2.86-3.00 (m 1 H), 3.70-3.84 (m, 4 H), 3.90-4.00(m. 1 H), 4.02-4.18 (m, 1 H), 4.36-4.52 (m, 2 H), 5.48-5.54 (m, 1 H), 5.72-5.78 (m, 1 H), 6.80-6.88 (m, 2 H), 7.18-7.28 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.93 (q'), 21.40 (t'), 28.19 (t'), 31.14 (t'), 33.49 (t'), 34.87 (t'), 41.95 (t'), 42.17 (t'), 51.06 (d'), 55.33 (q'), 67.68 (s'), 69.22 (t'), 70.52 (t'), 70.66 (t'), 71.53 (d'), 71.73 (d'), 113.83 (d'), 129.26 (d'), 130.65 (s'), 130.69 (s'), 130.86 (d'), 139.52 (d'), 159.21 (s'), 171.32 (s'), 171.37 (s'); exact mass *m/z* calcd for $C_{22}H_{32}NO_4$ 374.2333, found, 374.2329.

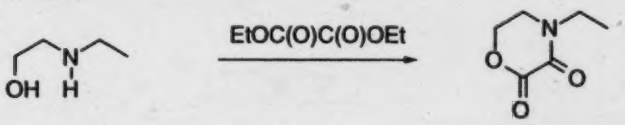
(6*R*,10*R*)-Hexahydro-6-spiro[cyclopent-2-ene-1,6'-pyrido[2,1-c][1,4]oxazine-3,4-dione (40.1).

21.1 **40.1**

EtO_2CCO_2Et (0.22 mL, 1.62 mmol) was added to a solution of **21.1** (0.181 g, 1.08 mmol) in PhMe (10 mL) and the mixture was refluxed overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 10 cm), using 70% EtOAc-hexane, gave **40.1** (0.139 g, 58%) as a white solid: mp 145-146 °C; $[\alpha]^{25}_D$ +1.54(*c* 1.56, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 1762, 1676 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.46 (m, 1 H), 1.52-1.98 (m, 6 H), 2.12-2.21 (m, 1 H), 2.24-

2.34 (m, 1 H), 2.48-2.58 (m, 1 H), 3.76-3.86 (m, 1 H), 4.14-4.24 (m, 1 H), 4.30-4.38 (m, 1 H), 5.68 (dt, J = 6.5, 2.6 Hz, 1 H), 6.04 (dt, J = 5.6, 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.97 (t'), 26.81 (t'), 30.48 (t'), 33.81 (t'), 35.00 (t'), 52.18 (d'), 69.17 (t'), 72.27 (s'), 127.29 (d'), 136.80 (d'), 154.34 (s'), 156.94 (s'); exact mass m/z calcd for $C_{12}H_{15}NO_3Na$ (M + Na) 244.0944, found, 244.0942.

4-Ethylmorpholine-2,3-dione (41.1).

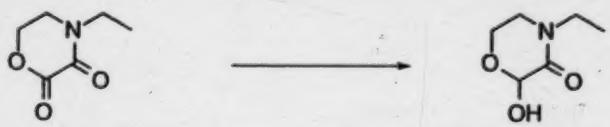


41.1

EtO_2CCO_2Et (1.40 mL, 10.3 mmol) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of 2-(ethylamino)ethanol (0.646 g, 7.25 mmol) in EtOH (10 mL). After 10 min, the ice bath was replaced by an oil bath, which was immediately switched on, and, after the mixture had refluxed for 10 min, the mixture was cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 25 cm), using 65% EtOAc-hexane, gave **41.1** (0.772 g, 74%) as a white solid: mp 76-77 °C; FTIR (CH_2Cl_2 cast) 1748, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 7.2 Hz, 3 H), 3.47 (q, J = 7.2 Hz, 2 H), 3.60-3.64 (m, 2 H), 4.43-4.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.00 (q'), 42.25 (t'), 44.30 (t'), 65.53

(t'), 153.26 (s'), 157.09 (s'); exact mass *m/z* calcd for $C_6H_9NO_3$ 143.0582; found, 143.0578.

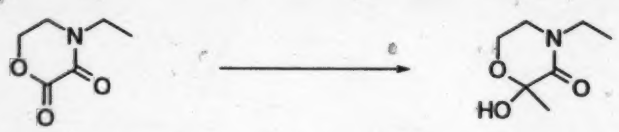
4-Ethyl-2-hydroxymorpholin-3-one (41.2).



41.1 **41.2**

DIBAL-H (1.0 M in hexane, 1.05 mL, 1.05 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **41.1** (0,125 g, 0.874 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued at -78 °C for 30 min, and $Na_2SO_4 \cdot 10H_2O$ (338 mg, 1.05 mmol) was then added in one portion. The cold bath was removed and stirring was continued for 1 h, during which time the mixture attained room temperature. The slurry was diluted with Et_2O (20 mL), and filtered through a pad of Celite (3.5 x 2 cm), which was rinsed with Et_2O (2 x 10 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 20 cm), using EtOAc, gave **41.2** (99 mg, 78%) as a white solid: mp 117-118 °C; FTIR (CH_2Cl_2 cast) 3169, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, *J* = 7.2 Hz, 3 H), 3.14-3.34 (m, 1 H), 3.38-3.60 (m, 3 H), 3.78-3.88 (m, 1 H), 4.22-4.32 (m, 1H), 5.22 (s, 1 H), 5.40-5.57 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.90 (q'), 41.58 (t'), 45.56 (t'), 57.81 (t'), 90.52 (d'), 166.37 (s'); exact mass *m/z* calcd for $C_6H_{11}NO_3$ 145.0739, found, 145.0741.

4-Ethyl-2-hydroxy-2-methylmorpholin-3-one (43.1).



41.1 **43.1**

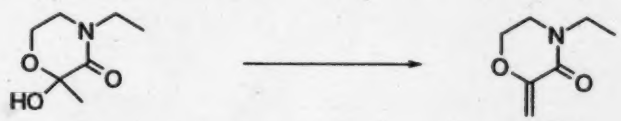
Method A

MeMgBr (3.0 M in Et_2O, 3.59 mL, 10.8 mmol) was added dropwise over 30 min to a stirred and cooled (-78 °C) solution of **41.1** (1.538 g, 10.8 mmol) in dry THF (50 mL). Stirring was continued at -78 °C for 1 h, and saturated aqueous NH_4Cl (20 mL) was added. Stirring was continued until the mixture had attained room temperature. The mixture was extracted with Et_2O (3 x 30 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 30 cm), using 50% EtOAc-hexane, gave **43.1** (1.310 g, 76%) as a white solid: mp 94-95 °C; FTIR (CH_2Cl_2 cast) 3337, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, J = 7.2 Hz, 3 H), 1.53 (s, 3 H), 3.02-3.10 (m, 1 H), 3.36 (q, J = 7.2 Hz, 2 H), 3.57 (dt, J = 11.8, 4.5 Hz, 1 H), 3.68-3.78 (m, 1 H), 4.22 (dt, J = 11.8, 3.4 Hz, 1 H), 4.39-4.52 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.84 (q'), 25.90 (q'), 41.75 (t'), 46.09 (t'), 57.65 (t'), 95.51 (s'), 168.23 (s'); exact mass m/z calcd for $C_7H_{13}NO_3$ 159.0895, found, 159.0893.

Method B

The above procedure was followed, using MeLi (1.4 M in Et_2O, 0.54 mL, 0.76 mmol), and **41.1** (0.108 g, 0.76 mmol) in dry THF (10 mL), to obtain **43.1** (72 mg, 60%) as a white solid.

4-Ethyl-2-methylenemorpholin-3-one (42.3).



43.1 **42.3**

$MeSO_2Cl$ (0.34 mL, 4.39 mmol) was added dropwise over 10 min to a stirred and cooled (0 °C) solution of **43.1** (140 mg, 0.881 mmol), Et_3N (1.84 mL, 13.2 mmol) and DMAP (ca 10 mg) in dry CH_2Cl_2 (20 mL). The ice bath was left in place but was not recharged, and stirring was continued for 2 h, during which (after ca 1 h) the mixture attained room temperature. The mixture was recooled and more $MeSO_2Cl$ (0.34 mL. 4.39 mmol) was added dropwise over 10 min at 0 °C. The ice bath was not recharged and stirring was continued for 6 h. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 50% EtOAc-hexane, gave starting material (36 mg, 26%) and the desired product **42.3** (81 mg,

65%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1663, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 7.2 Hz, 3 H), 3.42-3.50 (m, 4 H), 4.00-4.04 (m, 2 H), 4.72 (s, 1 H), 5.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.07 (q'), 41.85 (t'), 45.47 (t'), 63.69 (t'), 98.72 (d'), 151.05 (s'), 158.79 (s'); exact mass m/z calcd for $C_7H_{11}NO_2$ 141.0790, found, 141.0787.

4-Ethyl-2-hydroxy-2-[(phenylseleno)methyl]-morpholin-3-one (43.4).

42.3 **43.4**

PhSeCl (40 mg, 0.21 mmol) was added in one portion to a stirred solution of **42.3** (29 mg, 0.21 mmol) in a mixture of MeCN (5 mL) and water (1 mL). Stirring was continued for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 25 cm), using 50% EtOAc-hexane, gave **43.4** (42 mg, 64%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 3305, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 7.2 Hz, 3 H), 3.04-3.10 (m, 1 H), 3.28-3.53 (m, 4 H), 3.67 (dt, J = 12.0, 4.4 Hz, 1 H), 3.73-3.79 (m, 1 H), 3.89 (s, 1 H), 4.22 (dt, J = 11.8, 3.2 Hz, 1 H), 7.17-7.23 (m, 3 H),

7.50-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.14 (q'), 37.89 (t'), 42.23 (t'), 46.28 (t'), 58.32 (t'), 96.13 (s'), 126.99 (d'), 128.96 (d'), 130.23 (s'), 132.45 (d'), 166.25 (s'); exact mass *m/z* calcd for $C_{13}H_{17}NO_3{}^{80}Se$ 315.0374, found, 315.0372.

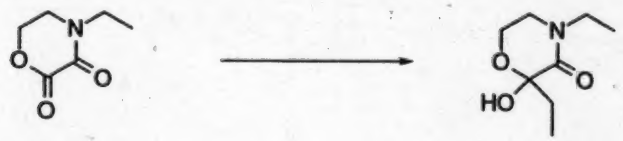
***N*-Ethyl-*N*-(2-hydroxyethyl)-2-hydroxy-3-(phenylseleno)propanamide (43.6).**

43.4 **43.6**

$NaBH_4$ (77 mg, 2.03 mmol) was added in portions over 10 min to a stirred and cooled (0 °C) solution of **43.4** (45 mg, 0.14 mmol) in MeOH (10 mL). After 20 min, the ice bath was removed, and stirring was continued for 3 h. The solvent was evaporated and the residue was redissolved in EtOAc (10 mL), and then washed with water, and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 10:60:30 MeOH-EtOAc-hexane, gave **43.6** (34 mg, 75%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3381, 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03-1.09 (m, 3 H), 2.62-2.84 (br, s, 1 H), 3.00-3.28 (m, 4 H), 3.28-3.38 (m, 1 H), 3.48-3.56 (m, 1 H), 3.58-3.78 (m, 2 H), 4.42-4.60 (m, 1 H), 7.21-7.27 (m, 3 H), 7.52-7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (mixture of rotamers) δ 12.50

(q'), 13.97 (q'), 33.10 (t'), 33.40 (t'), 41.14 (t'), 43.12 (t'), 48.33 (t'), 49.17 (t'), 59.82 (t'), 61.56 (t'), 67.40 (t'), 127.34 (d'), 127.54 (d'), 129.10 (d'), 129.16 (d'), 129.33 (s'), 129.67 (s'), 133.43 (d'), 133.57 (d'), 172.42 (s'), 173.66 (s'); exact mass *m/z* calcd for $C_{13}H_{19}NO_3{}^{80}Se$ 317.0530, found, 317.0530.

2,4-Diethyl-2-hydroxymorpholin-3-one (43.2).

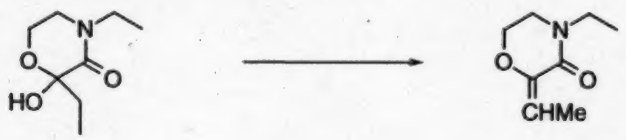


41.1 **43.2**

EtMgBr (1.0 M in Et_2O, 13.0 mL, 13.0 mmol), made from EtBr (4.36 g, 40 mmol) and Mg (1.15 g, 47 mmol) in Et_2O (40 mL), was added dropwise over 30 min to a stirred and cooled (-78 °C) solution of **41.1** (1.487 g, 10.4 mmol) in dry THF (50 mL). Stirring was continued at -78 °C for 1 h, and saturated aqueous NH_4Cl (20 mL) was then added. The cold bath was removed and stirring was continued for ca 1 h, during which time the mixture attained room temperature. The mixture was extracted with Et_2O (3 x 30 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 30 cm), using 50% EtOAc-hexane, gave **43.2** (1.380 g, 77%) as a white solid: mp 57-57.5 °C; FTIR (CH_2Cl_2 cast) 3343, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, J = 7.4

Hz, 3 H), 1.08 (t, J = 7.2 Hz, 3 H), 1.64 (m, 1 H), 1.85-2.02 (m, 1 H), 2.88-3.06 (m, 1 H), 3.18-3.32 (m, 1 H), 3.42-3.64 (m, 2 H), 3.70-3.78 (m, 1 H), 4.18 (dt, J = 11.8, 3.2 Hz, 1 H), 4.28 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 7.53 (q'), 12.03 (q'), 32.45 (t'), 41.89 (t'), 46.31 (t'), 58.04 (t'), 97.87 (s'), 168.01 (s'); exact mass m/z calcd for $C_8H_{15}NO_3$ 173.1052, found, 173.1048.

4-Ethyl-2-ethylidenemorpholin-3-one (43.3).



43.2 **43.3**

$MeSO_2Cl$ (2.04 mL, 26.4 mmol) was added dropwise over 30 min to a stirred and cooled (0 °C) solution of **43.2** (0.910 g, 5.26 mL), Et_3N (13.0 mL, 93.3 mmol) and DMAP (ca 10 mg) in CH_2Cl_2 (80 mL). After 10 min, the ice bath was removed, and stirring was continued overnight. Saturated aqueous NH_4Cl (20 mL) was then added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 50% EtOAc-hexane, gave **43.3** (0.775 g, 95%) as a thick, light yellow oil, which was a single isomer whose stereochemistry was not assigned: FTIR (CH_2Cl_2 cast) 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, J = 7.2 Hz, 3 H), 1.62

(d, J = 7.3 Hz, 3 H), 3.38-3.49 (m, 4 H), 3.99-4.05 (m, 2 H), 5.99 (q, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 10.27 (q'), 12.30 (q'), 41.83 (t'), 45.62 (t'), 63.71 (t'), 111.21 (d'), 145.04 (s'), 159.26 (s'); exact mass m/z calcd for $C_8H_{13}NO_2$ 155.0946, found, 155.0945.

4-Ethyl-2-hydroxy-2-[1-(phenylseleno)ethyl]-morpholin-3-one (43.5).

Method A

43.3 **43.5**

PhSeCl (67 mg, 0.35 mmol) was added in one portion to a stirred solution of **43.3** (27 mg, 0.17 mmol) in a mixture of MeCN (5 mL) and water (1 mL). Stirring was continued at room temperature overnight, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 50% EtOAc-hexane, gave **43.5** (52 mg, 90%) as a white solid, which was a mixture of two diastereoisomers: mp 80-81 °C; FTIR (CH_2Cl_2 cast) 3305, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11-1.17 (m, 3 H), 1.48 (d, J = 7.0, 1 H), 1.58 (d, J

= 7.2, 2 H), 3.02-3.10 (m, 1 H), 3.18-3.34 (m, 1 H), 3.50-3.68 (m, 1 H), 3.74-3.92 (m, 1 H), 4.12 (s, 0.3 H), 4.19 (dt, J = 11.9, 2.9 Hz, 0.7 H), 4.31 (dt, J = 11.9, 3.2 Hz, 0.3 H), 4.56 (s, 0.7 H), 7.16-7.25 (m, 3 H), 7.50-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 12.04 (q'), 12.17 (q'), 16.22 (q'), 18.81 (q'), 42.28 (t'), 42.42 (t'), 46.14 (t'), 46.38 (t'), 47.64 (d'), 51.98 (d'), 57.54 (t'), 58.95 (t'), 97.55 (s'), 97.88 (s'), 127.26 (d'), 127.63 (d'), 128.83 (d'), 128.95 (s'), 129.03 (d'), 130.23 (s'), 133.92 (d'), 134.10 (d'), 164.99 (s'), 168.12 (s'); exact mass m/z calcd for $C_{14}H_{19}NO_3{}^{80}Se$ 329.0530, found, 329.0631.

Method B

41.1 **43.5**

1,1-Bis(phenylseleno)ethane was made from PhSeH, MeCHO and $ZnCl_2$.[29]

BuLi (2.5 M in hexane, 0.088 mL, 0.22 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of 1,1-bis(phenylseleno)ethane (74 mg, 0.22 mmol) in THF (10 mL). Stirring was continued for 10 min at -78 °C. A solution of **41.1** (28 mg, 0.20 mmol) in THF (3 mL plus 1 mL as a rinse) was added over 10 min. The dry ice bath was left in place but was not recharged, and stirring was continued for

2.5 h, during which time (after ca 2 h) the mixture attained room temperature. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% EtOAc-hexane, gave **43.5** (46 mg, 70%) as a white solid, identical with material obtained by Method A.

***N*-Ethyl-*N*-(2-hydroxyethyl)-2-hydroxy-3-(phenylseleno)butanamide (43.7).**

43.5 **43.7**

$NaBH_4$ (126 mg, 3.33 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **43.5** (109 mg, 0.332 mmol) in MeOH (20 mL). The ice bath was not recharged, and stirring was continued for 2 h, during which time (after ca 1 h) the mixture attained room temperature. The solvent was evaporated and the residue was redissolved in EtOAc (10 mL), and washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% EtOAc-hexane, gave **43.7** (106 mg, 97%) as mixture of rotamers of two diastereoisomers. The material was a thick, colorless oil: FTIR (CH_2Cl_2 cast) 3395,

1632 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96-1.12 (m, 3 H), 1.28-1.56 (m, 3 H), 2.30-4.10 (m, 9 H), 4.28-4.58 (m, 1 H), 7.16-7.30 (m, 3 H), 7.48-7.66 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ (signals for component only) 12.66 (q'), 14.11 (q'), 20.19 (q'), 20.35 (q'), 41.11 (t'), 43.37 (t'), 44.23 (d'), 44.49 (d'), 48.71 (t'), 49.05 (t'), 59.68 (t'), 61.32 (t'), 71.59 (d'), 71.65 (d'), 127.65 (d'), 127.85 (d'), 128.32 (s'), 128.52 (s'), 128.85 (d'), 128.94 (d'), 135.17 (d'), 135.28 (d'), 171.79 (s'), 172.80 (s'); exact mass *m/z* calcd for $C_{14}H_{21}NO_3{}^{80}Se$ 331.0687, found, 331.0685.

(6*R*,10*R*)-Hexahydro-3-hydroxy-3-methyl-6-spiro-[cyclopent-2-ene-1,6'-pyrido[2,1-c][1,4]oxazin-4-one (45.1).

40.1 **45.1**

MeMgBr (3.0 M in Et_2O, 0.05 mL, 0.15 mmol) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of **40.1** (19 mg, 0.086 mmol) in THF (5 mL). The ice bath was not recharged and stirring was continued for 2 h, during which time (after ca 1 h) the mixture attained room temperature. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine, dried

($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 10 cm), using 50% EtOAc-hexane, gave **45.1** (isomer A, 8.9 mg, 44%) and isomer B (9.4 mg, 46%) as colorless oils. Isomer A had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16-1.32 (m, 1 H), 1.52 (s, 3 H), 1.44-1.94 (m, 6 H), 2.16-2.32 (m, 2 H), 2.42-2.54 (m, 1 H), 3.03 (s, 1 H), 3.56-3.72 (m, 2 H), 3.86-3.98 (m, 1 H), 5.55-5.60 (m, 1 H), 6.12-6.17 (m, 1 H). Isomer B had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (s, 3 H), 1.40-1.98 (m, 7 H), 2.16-2.32 (m, 2 H), 2.42-2.54 (m, 1 H), 3.30 (d, *J* = 1.8 Hz, 1 H), 3.34-3.42 (m, 1 H), 3.59 (dd, *J* = 12.1, 2.4 Hz, 1 H), 4.17 (dd, *J* = 12.1, 4.4 Hz, 1 H), 5.60-5.66 (m, 1 H), 6.09-6.14 (m, 1 H).

(6*R*,10*R*)-Hexahydro-3-hydroxy-3-[1-(phenylseleno)-ethyl]-6-spiro[cyclopent-2-ene-1,6'-pyrido[2,1-c]-[1,4]oxazin-4-one (47.1).

40.1 **47.1**

BuLi (2.5 M in hexane, 0.15 mL, 0.38 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of 1,1-bis(phenylseleno)ethane (127 mg, 0.37 mmol) in THF (10 mL). Stirring was continued for 10 min at -78 °C, and a solution of **40.1** (53 mg, 0.24 mmol) in THF (5 mL plus 2 mL as a rinse) was added dropwise over 10 min at -78 °C. Stirring

was continued for 30 min at -78 °C and then saturated aqueous NH_4Cl (5 mL) was added. The cold bath was removed and stirring was continued for 30 min, during which time the mixture attained room temperature. The mixture was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 20% EtOAc-hexane, gave four isomers of **47.1** [isomer A (8.1 mg, 8.3%); isomer B (5.1 mg, 5.2%), isomer C (33.5 mg, 34.4%), isomer D (41.1 mg, 42.2%)] as thick, colorless oils. Isomer A had: FTIR (CH_2Cl_2 cast) 3312, 3055, 1660, 1631, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16-1.32 (m, 1 H), 1.49 (d, J = 7.1 Hz, 3 H), 1.40-1.88 (m, 6 H), 2.18-2.30 (m, 2 H), 2.38-2.50 (m, 1 H), 3.56-3.65 (m, 1 H), 3.67 (dd, J = 11.8, 4.3 Hz, 1 H), 3.92 (s, 1 H), 3.97 (q, J = 7.1 Hz, 1 H), 4.04 (dd, J = 11.8, 10.7 Hz, 1 H), 5.48-5.56 (m, 1 H), 6.16-6.22 (m, 1 H), 7.18-7.28 (m, 3 H), 7.52-7.59 (m, 2 H); exact mass m/z calcd for $C_{20}H_{25}NNaO_3{}^{80}Se$ (M + Na) 430.0892, found, 430.0891.

Isomer B had: FTIR (CH_2Cl_2 cast) 3315, 2931, 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14-1.30 (m, 1 H), 1.57 (d, J = 7.2 Hz, 3 H), 1.44-1.82 (m, 4 H), 2.04-2.48 (m, 5 H), 3.43 (d, J = 8.7 Hz, 1 H), 3.59 (q, J = 7.2 Hz, 1 H), 3.72-3.82 (m, 2 H), 3.83-3.92 (m, 1 H), 5.55-5.63 (m, 1 H), 6.12-6.20 (m, 1 H), 7.14-7.28 (m, 3 H), 7.48-7.60 (m, 2 H); exact mass m/z calcd for $C_{20}H_{25}NNaO_3{}^{80}Se$ (M + Na) 430.0892, found, 430.0894.

Isomer C had: FTIR (CH_2Cl_2 cast) 3315, 3053, 1657, 1630, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57 (d, J = 7.1

Hz, 3 H), 1.46-2.06 (m, 7 H), 2.14-2.30 (m, 2 H), 2.42-2.54 (m, 1 H), 3.32-3.41 (m, 1 H), 3.55 (dd, J = 12.1, 0.6 Hz, 1 H), 3.84 (s, 1 H), 3.91 (q, J = 7.1 Hz, 1 H), 4.39 (dd, J = 12.1, 4.1, 1 H), 5.60-5.66 (m, 1 H), 6.12-6.20 (m, 1 H), 7.18-7.28 (m, 3 H), 7.52-7.62 (m, 2 H); exact mass m/z calcd for $C_{20}H_{25}NNaO_3{}^{80}Se$ (M + Na) 430.0892, found, 430.0893.

Isomer D had: FTIR (CH_2Cl_2 cast) 3309, 2933, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38-1.46 (m, 1 H), 1.60 (d, J = 7.1 Hz, 3 H), 1.54-1.66 (m, 1 H), 1.70-1.96 (m, 4 H), 2.16-2.32 (m, 3 H), 2.42-2.53 (m, 1 H), 3.30-3.38 (m, 1 H), 3.61 (dq, J = 7.1, 1.1 Hz, 1 H), 3.64 (d, J = 12.2 Hz, 1 H), 3.76 (d, J = 13.1 Hz, 1 H), 4.27 (dd, J = 12.2, 3.9 Hz, 1 H), 5.58-5.64 (m, 1 H), 6.16-6.22 (m, 1 H), 7.18-7.30 (m, 3 H), 7.55-7.62 (m, 2 H); exact mass m/z calcd for $C_{20}H_{25}NNaO_3{}^{80}Se$ (M + Na) 430.0892, found, 430.0895.

4-Ethyl-2-hydroxy-2-[(trimethylsilyl)ethynyl]-morpholin-3-one (48.1).

41.1 **48.1**

BuLi (2.5 M in hexane, 0.40 mL, 1.0 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of (trimethylsilyl)acetylene (97 mg, 0.99 mmol) in dry THF (5 mL). Stirring was continued at -78 °C for 30 min, and a

solution of **41.1** (0.129 g, 0.902 mmol) in THF (3 mL plus 1 mL as a rinse) was added dropwise over 10 min. Stirring was continued for 30 min at -78 °C, and saturated aqueous NH_4Cl (5 mL) was then added. Stirring was continued until the mixture had attained room temperature, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% EtOAc-hexane, gave **48.1** (0.155 g, 72%) as a white solid: mp 106-107 °C; FTIR (CH_2Cl_2 cast) 3270, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 6 H), 1.13 (t, J = 7.2 Hz, 3 H), 3.26-3.52 (m, 4 H), 4.00-4.18 (m, 2 H), 4.52 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -0.45 (q'), 11.74 (q'), 42.30 (t'), 45.55 (t'), 59.15 (t'), 89.57 (s'), 90.59 (s'), 101.45 (s'), 164.91 (s'); exact mass m/z calcd for $C_{11}H_{19}NO_3Si$ 241.1134, found, 241.1131.

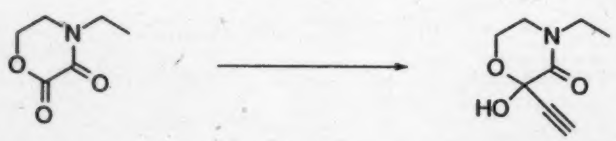
***N*-Ethyl-*N*-(2-hydroxyethyl) 2-Hydroxy-4-(trimethylsilyl)-3-butynamide (42.1).**

48.1 **42.1**

$NaBH_4$ (13 mg, 0.34 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **48.1** (40 mg, 0.17 mmol) in MeOH (5 mL). The ice bath was not recharged and stirring

was continued for 2 h, during which time (after ca 1 h) the mixture attained room temperature. Hydrochloric acid (1 M) was added until the pH = 2, and the solvent was evaporated. The residue was redissolved in EtOAc, washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (1.3 x 20 cm), using 50% EtOAc-hexane, gave **42.1** (32 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3387, 2173, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13-0.16 (m, 6 H), 1.15 (t, J = 7.1 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 2 H), 2.00-3.00 (br, 1 H), 3.24-3.38 (m, 1 H), 3.40-3.50 (m, 2 H), 3.60-3.70 (m, 1 H), 3.70-3.86 (m, 2 H), 4.31 (s, 1 H), 4.90 (s, 0.7 H), 5.00 (s, 0.3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -0.41 (q'), -0.38 (q'), 12.13 (q'), 13.16 (q'), 41.73 (t'), 42.79 (t'), 48.09 (t'), 49.19 (t'), 59.92 (t'), 60.02 (d'), 60.10 (d'), 61.27 (t'), 90.83 (s'), 90.98 (s'), 100.96 (s'), 101.42 (s'), 169.01 (s'), 169.79 (s'); exact mass m/z calcd for $C_{11}H_{21}NO_3Si$ 243.1291, found, 243.1296.

4-Ethyl-2-ethynyl-2-hydroxymorpholin-3-one (49.1).



41.1 **49.1**

Method A

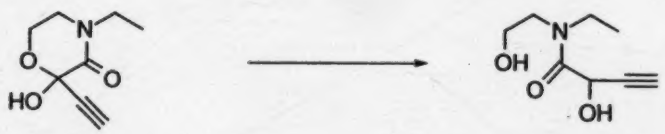
BuLi (2.5 M in hexane, 0.86 mL, 2.15 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of (trimethylsilyl)acetylene (210 mg, 2.14 mmol) in dry THF (10 mL). Stirring was continued at -78 °C for 30 min, and a solution of **41.1** (0.255 g, 1.78 mmol) in THF (6 mL plus 1 mL as a rinse) was added dropwise over 10 min. Stirring was continued at -78 °C for 30 min. MeOH (2 mL) and saturated aqueous $NaHCO_3$ (1 drop) were added, and stirring was continued until the mixture attained room temperature. The mixture was extracted with EtOAc (2 x 10 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 50% EtOAc-hexane, gave **49.1** (0.128 g, 42%) as a thick, light yellow oil: FTIR (CH_2Cl_2 cast) 3255, 2121, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.2 Hz, 3 H), 2.62 (s, 1H), 3.31-3.38 (m, 1 H), 3.44 (q, J = 7.2 Hz, 2 H), 3.45-3.53 (m, 1 H), 4.02-4.10 (m, 1 H), 4.14-4.22 (m, 1 H), 5.05 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.72 (q'), 42.37 (t'), 45.55 (t'), 59.04 (t'), 73.46 (d'), 80.57 (s'), 89.54 (s'), 164.74 (s'); exact mass m/z calcd for $C_8H_{11}NO_3$ 169.0739, found, 169.0737.

Method B

Ethynylmagnesium bromide (0.5 M in THF, 0.89 mL, 0.45 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **41.1** (61 mg, 0.43 mmol) in dry THF (5

mL). Stirring was continued at -78 °C for 30 min, and saturated aqueous NH_4Cl (5 mL) was added. The mixture was allowed to warm to room temperature, and then extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% EtOAc-hexane, gave **49.1** (37 mg, 51%) as a thick, light yellow oil, identical to material made by method A.

***N*-Ethyl-*N*-(2-hydroxyethyl)-2-hydroxy-3-butynamide (48.2).**



49.1 **48.2**

$NaBH_4$ (29 mg, 0.77 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **49.1** (0.129 g, 0.76 mmol) in MeOH (10 mL). The ice bath was not recharged and stirring was continued for 2 h, during which time (after ca 1 h) the mixture attained room temperature. Hydrochloric acid (1 M) was added until the pH = 2. The solvent was evaporated, and the residue was redissolved in EtOAc (10 mL). The solution was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% EtOAc-hexane, gave **48.2** (65 mg, 50%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 3283,

2114, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.2 Hz, 1 H), 1.23 (t, J = 7.2 Hz, 2 H), 2.20-3.00 (br, s, 1 H), 2.51 (d, J = 2.3 Hz, 0.5 H), 2.54 (d, J = 2.3 Hz, 0.5 H), 3.18-3.32 (m, 1 H), 3.35-3.46 (m, 1 H), 3.50-3.61 (m, 1 H), 3.64-3.84 (m, 3 H), 4.20-4.50 (br, s, 1 H), 4.89 (d, J = 2.3 Hz, 0.6 H), 5.08 (d, J = 2.3 Hz, 0.4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.21 (q'), 13.26 (q'), 41.76 (t'), 42.81 (t'), 48.25 (t'), 49.12 (t'), 59.28 (d'), 59.39 (d'), 59.70 (t'), 61.01 (t'), 73.81 (d'), 74.03 (d'), 79.99 (s'), 80.22 (s'), 168.87 (s'), 169.46 (s'); exact mass m/z calcd for $C_8H_{14}NO_3$ (M + H) 172.0968, found, 172.0967.

(6*R*,10*R*)-3-Ethynylhexahydro-3-hydroxy-6-spiro-[cyclopent-2-ene-1,6'-pyrido[2,1-c][1,4]oxazin-4-one (50.1).

40.1 **50.1**

Ethynylmagnesium bromide (0.5 M in THF, 0.69 mL, 0.35 mmol) was added over 5 min to a stirred and cooled (0 °C) solution of **40.1** (64 mg, 0.29 mmol) in THF (10 mL). The ice bath was not recharged and stirring was continued for 2 h, during which time (after ca 1 h) the mixture attained room temperature. Saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with Et_2O (2 x 20 mL). The

combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 50% EtOAc-hexane, gave **50.1** (64 mg, 90%) as a thick, colorless oil, which was a mixture of two diastereoisomers: FTIR (CH_2Cl_2 cast) 3259, 2118, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28-2.00 (m, 7 H), 2.12-2.32 (m, 2 H), 2.43-2.54 (m, 1 H), 2.58 (s, 0.5 H), 2.66 (s, 0.5 H), 3.53-3.70 (m, 1 H), 3.82-3.88 (m, 0.5 H), 3.95-4.08 (m, 1.5 H), 4.44 (s, 0.5 H), 4.88 (s, 0.5 H), 5.56-5.61 (m, 0.5 H), 5.61-5.65 (m, 0.5 H), 5.95-6.02 (m, 0.5 H), 6.19-6.25 (m, 0.5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.56 (t'), 19.97 (t'), 27.77 (t'), 28.05 (t'), 30.10 (t'), 30.27 (t'), 32.33 (t'), 33.90 (t'), 34.78 (t'), 34.97 (t'), 53.85 (d'), 54.61 (d'), 64.59 (t'), 65.13 (t'), 71.47 (s'), 72.25 (s'), 73.04 (d'), 74.42 (d'), 80.79 (s'), 80.96 (s'), 89.50 (s'), 90.28 (s'), 124.73 (d'), 126.87 (d'), 136.92 (d'), 137.91 (d'), 165.33 (s'), 166.80 (s'); exact mass *m/z* calcd for $C_{14}H_{17}NO_3Na$ (M + Na) 270.1106, found, 270.1102.

1-(2,3-Dihydroindol-1-yl)-2-[(5*R*,7*R*)-(7-hydroxymethyl)-6-azaspiro[4,5]dec-1-ene-6-yl]ethane-1,2-dione (54.1).

40.1 **54.1**

MeMgBr (3.0 M in Et_2O, 0.10 mL, 0.30 mmol) was added dropwise over 5 min to a stirred and cooled (-10 °C) solution of indoline (36 mg, 0.30 mmol) in THF (10 mL). Stirring was continued for 20 min at -10 °C, and a solution of **40.1** (33 mg, 0.15 mmol) in THF (2 mL plus 1 mL as a rinse) was then added dropwise over 10 min. Stirring was continued for another 30 min and saturated aqueous NH_4Cl (5 mL) was added. The cold bath was removed and stirring was continued for 30 min, during which time the mixture attained room temperature. The mixture was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% EtOAc-hexane, gave what is assumed to be **54.1** (36 mg, 70%) as a white solid: mp 150-151 °C; FTIR (CH_2Cl_2 cast) 3406, 1651, 1644, 1596 cm^{-1}; exact mass *m/z* calcd for $C_{20}H_{24}N_2O_3Na$ (M + Na) 363.1679, found, 363.1671.

1-(2,3-Dihydroindol-1-yl)-2-[(5*R*,7*R*)-7-[[[tris(1-methylethyl)silyl]oxy]methyl]-6-azaspiro[4,5]dec-1-ene-6-yl]ethane-1,2-dione (54.2).

54.1 **54.2**

i-Pr_3SiCl (0.06 mL, 54 mg, 0.28 mmol) was added dropwise over 5 min to a stirred solution of **54.1** (35 mg, 0.10 mmol), imidazole (21 mg, 0.19 mmol) and DMAP (4 mg, 0.033 mmol) in DMF (2 mL). Stirring was continued for 4 h, and saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with Et_2O (2 x 10 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 20% EtOAc-hexane, gave what is assumed to be **54.2** (50 mg, 98%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 2941, 2865, 1651, 1626, 1599 cm^{-1}; exact mass *m/z* calcd for $C_{29}H_{45}N_2O_3Si$ (M + H) 497.3194, found, 497.3198.

(2*R*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]methyl]-1-(phenylmethyl)-6-(2-propenyl)piperidin-2-yl]methyl 2,2-Dimethylpropanoate (55.2).

55.1 **55.2**

t-BuMe_2SiCl (0.308 g, 2.04 mmol) was added in one portion to a stirred solution of **55.1** (obtained as reported[4]) (0.367 g, 1.02 mmol), imidazole (0.278 g, 4.08 mmol) and DMAP (62 mg, 0.51 mmol) in DMF (6 mL). Stirring was continued at room temperature for 2 h and saturated aqueous NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (2 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 1% EtOAc-hexane, gave **55.2** (0.474 g, 98%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 2955, 2930, 2857, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.18 (s, 3 H), -0.08 (s, 3 H), 0.81 (s, 9 H), 1.11 (s, 9 H), 1.19-2.09 (m, 6 H), 2.47 (dq, J = 13.5, 8.1 Hz, 2 H), 2.66-2.95 (m, 1 H), 3.51 (AB q, J_{AB} = 10.4 Hz, Δ_{AB} = 38.6 Hz, 2 H), 3.68 (dd, J = 11.0, 7.8 Hz, 1 H), 3.80 (d, J = 17.0 Hz, 1 H), 4.13 (dd, J = 10.9, 3.6 Hz, 1 H), 4.09 (d, J = 17.0 Hz, 1 H), 5.00-5.12 (m, 2 H), 5.77-5.91 (m, 1 H), 7.10-7.16 (m, 1 H), 7.21-7.26 (m, 2 H), 7.32-7.39 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -2.98 (q'), 18.01 (s'), 18.09 (s'), 25.67

(q'), 25.75 (q'), 27.11 (q'), 29.01 (t'), 31.22 (t'), 34.18 (t'), 38.58 (s'), 51.66 (s'), 56.31 (d'), 59.81 (t'), 65.65 (t'), 69.62 (t'), 116.83 (t'), 125.85 (d'), 126.82 (d'), 127.89 (d'), 135.43 (d'), 143.20 (s'), 178.15 (s'); exact mass *m/z* calcd for $C_{28}H_{48}NO_3Si$ (M + H) 474.3398, found, 474.3398.

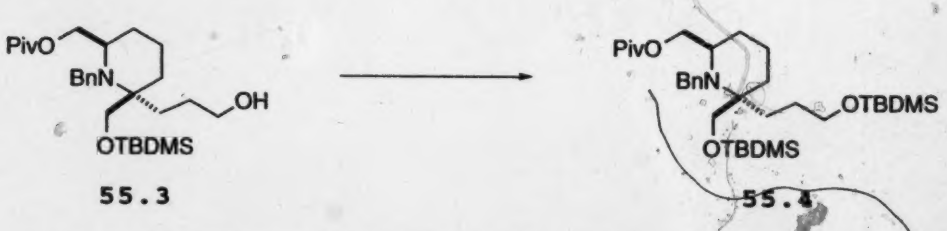
(2*R*,6*R*)-[6-[[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]methyl]-6-(3-hydroxypropyl)-1-(phenylmethyl)-piperidin-2-yl]methyl 2,2-Dimethylpropanoate (55.3).

55.2 **55.3**

9-BBN (0.5 M in THF, 3.10 mL, 1.55 mmol) was added dropwise over 10 min to a stirred and cooled (0 °C) solution of **55.2** (0.454 g, 0.96 mmol) in THF (20 mL). The ice bath was not recharged and stirring was continued overnight. The mixture was recooled to 0 °C, MeOH (3.3 mL), NaOH (2 M, 7.7 mL) and H_2O_2 (30%, 0.91 mL) were added successively and, after 30 min (stirring), the ice bath was replaced by a water bath at room temperature. Stirring was continued for 2 h. The mixture was extracted with Et_2O (2 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 20 cm), using 10% EtOAc-hexane, gave **55.3** (0.424

g, 90%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 3435, 2953, 2857, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -0.18 (s, 3 H), -0.08 (s, 3 H), 0.79 (s, 9 H), 1.09 (s, 9 H), 1.30-1.80 (m, 11 H), 2.90-3.00 (m, 1 H), 3.47 (AB q, J_{AB} = 10.3 Hz, Δ_{AB} = 33.7 Hz, 2 H), 3.58-3.64 (m, 2 H), 3.68 (dd, J = 11.0, 7.6 Hz, 1 H), 3.75 (d, J = 17.1, 1 H), 4.10 (dd, J =11.2, 4.0 Hz, 1 H), 4.30 (d, J = 17.1 Hz, 1 H), 7.09-7.15 (m, 1 H), 7.20-7.25 (m, 2 H), 7.32-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -5.92 (q'), 18.51 (s'), 25.43 (t'), 25.83 (t'), 25.86 (q'), 27.22 (q'), 27.38 (t'), 28.45 (t'), 30.57 (t'), 51.09 (s'), 55.98 (d'), 59.78 (t'), 63.80 (t'), 65.86 (t'), 69.78 (t'), 125.86 (d'), 126.74 (d'), 127.90 (d'), 143.11 (s'), 178.11 (s'); exact mass m/z calcd for $C_{28}H_{50}NO_4Si$ (M + H) 492.3504, found, 492.3502.

(2*R*,6*R*)-[6-[[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]methyl]-6-[3-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]propyl]-1-(phenylmethyl)piperidin-2-yl]methyl 2,2-Dimethylpropanoate (55.4).

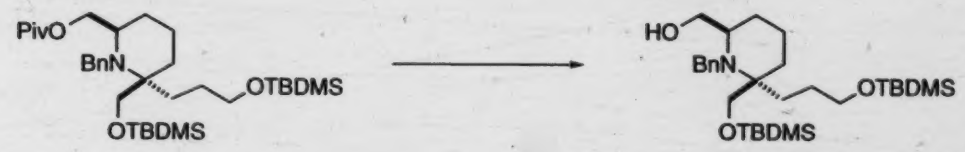


55.3 **55.4**

t-$BuMe_2SiCl$ (0.253 g, 1.68 mmol) was added in one portion to a stirred solution of **55.3** (0.413 g, 0.84 mmol), imidazole (0.229 g, 3.36 mmol) and DMAP (51 mg, 0.42 mmol) in

DMF (10 mL). Stirring was continued for 2 h and saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O (2 x 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 5% EtOAc-hexane, gave **55.4** (0.446 g, 88%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 2955, 2857, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ -0.19 (s, 3 H), -0.08 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.79 (s, 9 H), 0.86 (s, 9 H), 1.08 (s, 9 H), 1.20-1.80 (m, 10 H), 2.84-2.96 (m, 1 H), 3.38-3.64 (m, 4 H), 3.64-3.82 (m, 2 H), 4.10 (dd, J = 11.1, 3.7 Hz, 1 H), 4.30 (d, J = 17.0, 1 H), 7.07-7.14 (m, 1 H), 7.17-7.25 (m, 2 H), 7.30-7.37 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.94 (q'), -5.29 (q'), 18.04 (s'), 18.27 (s'), 25.47 (t'), 25.78 (q'), 25.96 (q'), 27.12 (q'), 27.33 (t'), 28.68 (t'), 30.67 (t'), 38.61 (s'), 51.20 (s'), 55.94 (d'), 59.54 (t'), 63.98 (t'), 65.64 (t'), 69.78 (t'), 69.84 (t'), 125.82 (t'), 126.86 (t'), 127.90 (t'), 143.34 (s'), 178.24 (s'); exact mass *m/z* calcd for $C_{34}H_{64}NO_4Si_2$ (M + H) 606.4374, found, 606.4380.

(2*R*,6*R*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]methyl]-6-[3-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]propyl]-1-(phenylmethyl)piperidine-2-methanol (55.5).



55.4 **55.5**

$LiAlH_4$ (48 mg, 1.3 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **55.4** (0.381 g, 0.63 mmol) in Et_2O (20 mL). The ice bath was not recharged and stirring was continued for 2 h, during which time (after ca 1 h) the mixture attained room temperature. The mixture was recooled to 0 °C, and $Na_2SO_4 \cdot 10H_2O$ (0.407 g, 1.3 mmol) was added. The ice bath was removed and stirring was continued for 1 h. The mixture was filtered through a pad of Celite (3.5 x 3 cm), using Et_2O (2 x 10 mL) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 10% EtOAc-hexane, gave **55.5** (0.282 g, 86%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3432, 2953, 2929, 2885, 2857 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.14 (s, 3 H), -0.03 (s, 3 H), 0.06 (s, 6 H), 0.79 (s, 9 H), 0.91 (s, 9 H), 1.20-1.80 (m, 11H), 2.68-2.76 (m, 1 H), 3.16-3.26 (m, 1 H), 3.40 (d, J = 16.7 Hz, 1 H), 3.45-3.54 (m, 1 H), 3.54-3.70 (m, 4 H), 4.57 (d, J = 16.7 Hz, 1 H), 7.14-7.21 (m, 1 H), 7.26-7.32 (m, 2 H), 7.41-7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$,

100.6 MHz) δ -5.89 (q'), -5.24 (q'), 18.04 (s'), 18.37 (s'), 18.86 (t'), 23.01 (t'), 25.73 (q'), 25.99 (q'), 27.71 (t'), 28.17 (t'), 30.74 (s'), 52.59 (t'), 60.06 (d'), 63.99 (t'), 64.15 (t'), 70.57 (t'), 126.33 (d'), 126.49 (d'), 128.55 (d'), 144.03 (s'); exact mass *m/z* calcd for $C_{29}H_{56}NO_3Si_2$ (M + H) 522.3793, found, 522.3795.

(6*R*,10*R*)-[6-[[3-(2,2-Dimethyl-1-oxopropyl)oxy]-propyl]-3,4-dioxohexahydropyrido[2,1-c][1,4]oxazin-6-yl]methyl 2,2-Dimethylpropanoate (56.1).

19.2 **56.1**

EtO_2CCO_2Et (0.32 mL, 2.31 mmol) was added over 5 min to a stirred solution of **19.2** (0.716 g, 1.93 mmol) in dry PhMe (20 mL), and the solution was refluxed overnight. The mixture was cooled to room temperature, and another portion of EtO_2CCO_2Et (0.2 mL) was injected. The mixture was refluxed until the starting material was completely consumed (TLC control). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 50% EtOAc-hexane, gave **56.1** (0.323 g, 39%) as a white solid: mp 112-113 °C; FTIR (CH_2Cl_2 cast) 2970, 1768, 1728, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14-1.20 (m, 18 H), 1.30-1.94 (m, 9 H), 2.14-2.24 (m, 1 H), 3.86-3.96 (m, 1 H),

3.96-4.06 (m, 2 H), 4.09-4.18 (m, 1 H), 4.31 (dd, J = 11.8, 3.1 Hz, 1 H), 4.36 (d, J = 11.0 Hz, 1 H), 4.75 (d, J = 10.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.13 (t'), 23.17 (t'), 25.03 (t'), 27.14 (q'), 29.31 (t'), 38.70 (s'), 38.78 (s'), 51.36 (d'), 62.00 (s'), 63.73 (t'), 67.17 (t'), 69.50 (t'), 154.63 (s'), 156.89 (s'), 177.62 (s'), 178.38 (s'); exact mass *m/z* calcd for $C_{22}H_{35}NO_7Na$ (M + Na) 448.2306, found, 448.2305.

(2*R*,6*R*)-[1-(Phenylmethyl)-2-[(triethylsilyl)oxy]-propyl]-6-[[[tris(1-methylethyl)silyl]oxy]methyl]-piperidin-2-yl]methyl 2,2-Dimethyl Propanoate (57.1).

18.4 **57.1**

Et_3SiOTf (0.14 mL, 0.62 mmol) was added dropwise over 10 min to a stirred and cooled (0 °C) solution of **18.4** (324 mg, 0.61 mmol) and *i*-Pr_2NEt (0.22 mL, 1.26 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 1 h at 0 °C and then brine (10 mL) was added. The cold bath was removed and stirring was continued for 30 min, during which time the mixture attained room temperature. The mixture was extracted with Et_2O (2 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane,

gave **57.1** (365 mg, 93%) as a colorless, thick oil: $[\alpha]^{25}_D$ 2.01 (*c* 1.54, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 2955, 2867, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.48-0.66 (m, 6 H), 0.84-1.02 (m, 30 H), 1.16 (s, 9 H), 1.20-1.90 (m, 10 H), 2.78-2.88 (m, 1 H), 3.22 (dd, J = 9.3, 8.7 Hz, 1 H), 3.54-3.63 (m, 2 H), 3.66 (dd, J = 9.5, 3.4 Hz, 1 H), 3.78 (d, J = 16.8 Hz, 1 H), 3.98 (AB q, J_{AB} = 11.7 Hz, Δ_{AB} = 13.3 Hz, 2 H), 4.13 (d, J = 16.3 Hz, 1 H), 7.09-7.16 (m, 1 H), 7.19-7.27 (m, 2 H), 7.30-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.43 (t'), 6.76 (d'), 11.81 (q'), 17.92 (q'), 22.64 (t'), 26.56 (t'), 27.13 (q'), 27.32 (t'), 28.33 (t'), 30.90 (t'), 38.77 (s'), 51.58 (s'), 58.47 (t'), 59.13 (d'), 63.38 (t'), 65.35 (t'), 70.31 (t'), 125.99 (d'), 126.74 (d'), 127.96 (d'), 142.83 (s'), 178.20 (s'); exact mass *m/z* calcd for $C_{37}H_{70}NO_4Si_2$ (M + H) 648.4838, found, 648.4838.

(2*R*,6*R*)-[1-(Phenylmethyl)-2-[(triethylsilyl)oxy]-propyl]-6-[[[tris(1-methylethyl)silyl]oxy]methyl]-piperidine-2-methanol (59.1).

57.1 **59.1**

DIBAL-H (1.0 M in hexane, 0.57 mL, 0.57 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **57.1** (355 mg, 0.55 mmol) in Et_2O (20 mL).

Stirring was continued for 30 min at -78 °C, and then $Na_2SO_4 \cdot 10H_2O$ (184 mg, 0.57 mmol) was added in one portion. The dry ice bath was removed and stirring was continued for 1 h, during which time the mixture attained room temperature. The resulting slurry was filtered through a pad of Celite (3.5 x 3 cm), using Et_2O (2 x 10) as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 25 cm), using 5% EtOAc-hexane, gave **59.1** (216 mg, 70%) as a colorless, thick oil: $[\alpha]^{25}_D$ 2.16 (*c* 1.3.9, CH_2Cl_2); FTIR (CH_2Cl_2 cast) 3456, 2943, 2866, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.61 (q, *J* = 7.9 Hz, 6 H), 0.90 (s, 21 H), 0.97 (t, *J* = 7.9 Hz, 9 H), 1.18-1.70 (m, 7 H), 1.70-1.84 (m, 1 H), 1.84-1.96 (m, 1 H), 1.96-2.05 (m, 1 H), 2.71 (s, 1 H), 2.76-2.87 (m, 1 H), 3.10-3.20 (m, 1 H), 3.29 (d, *J* = 11.1 Hz, 1 H), 3.44-3.68 (m, 5 H), 4.16 (d, *J* = 16.7 Hz, 1 H), 7.11-7.18 (m, 1 H), 7.22-7.34 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.41 (t'), 6.74 (d'), 11.72 (q'), 17.816 (q'), 17.824 (q'), 18.57 (t'), 24.21 (t'), 27.52 (t'), 28.95 (t'), 29.79 (t'), 51.79 (s'), 60.48 (d'), 60.78 (t'), 63.32 (t'), 66.93 (t'), 67.99 (t'), 126.29 (d'), 126.49 (d'), 128.34 (d'), 142.73 (s'); exact mass *m/z* calcd for $C_{32}H_{62}NO_3Si_2$ (M + H) 564.4263, found, 564.4263.

(2*R*,6*R*)-2-[[(Triethylsilyl)oxy]propyl]-6-[[[tris(1-methylethyl)silyl]oxy]methyl]piperidine-2-methanol (59.2).

59.1 **59.2**

1,4-Cyclohexadiene (0.40 mL, 4.23 mmol) was added to a suspension of **59.1** (216 mg, 0.38 mmol) and 10% Pd-C (64 mg) in EtOAc (10 mL). The mixture was warmed to 50 °C and stirred at this temperature overnight. The mixture was cooled to room temperature and filtered through a pad of Celite (3.5 x 4 cm), using EtOAc (2 x 10 mL) as a rinse. The filtrate was concentrated, giving **59.2** (170 mg, 94%) as a thick, colorless oil: FTIR (CH_2Cl_2 cast) 3319, 2942, 2866, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.50-0.62 (m, 6 H), 0.84-0.98 (m, 9 H), 0.98-1.10 (m, 21 H), 1.16-1.80 (m, 10 H), 2.98-3.14 (m, 1 H), 3.40-4.14 (m, 7 H), 4.40-5.80 (br, s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.35 (t'), 6.70 (d'), 11.81 (q'), 17.91 (q'), 18.77 (t'), 26.38 (t'), 27.17 (t'), 28.20 (t'), 52.51 (d'), 57.79 (s'), 60.29 (s'), 62.63 (t'), 65.71 (t'), 66.17 (t'), 66.60 (t'), 66.83 (t'); exact mass *m/z* calcd for $C_{25}H_{56}NO_3Si_2$ (M + H) 474.3793, found, 474.3792.

(2*R*,6*R*)-[1-(Phenylmethyl)-2-[(triethylsilyl)oxy]-propyl]-6-[[[tris(1-methylethyl)silyl]oxy]methyl]-piperidine-2-carbaldehyde (60.1).

59.1 **60.1**

Dess-Martin periodinane (51 mg, 0.12 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **59.1** (45 mg, 0.080 mmol) and pyridine (0.04 mL, 0.50 mmol) in CH_2Cl_2 (5 mL). The ice bath was left in place but was not recharged and stirring was continued for 1 h, during which time the mixture attained room temperature. Aqueous $Na_2S_2O_3$ (10%, 5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added successively. The mixture was stirred for 10 min, and extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.3 x 15 cm), using 5% EtOAc-hexane, gave **60.1** (40 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2953, 2866, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.57 (q, J = 8.0 Hz, 6 H), 0.91 (s, 21 H), 0.94 (t, J = 8.0 Hz, 9 H), 1.30-2.00 (m, 10 H), 2.82-2.92 (m, 1 H), 3.11 (t, J = 9.1 Hz, 1 H), 3.52-3.68 (m, 3 H), 3.82 (q, J = 16.4 Hz, 2 H), 7.13-7.18 (m, 1 H), 7.22-7.28 (m, 2 H), 7.32-7.37 (m, 2 H), 9.51 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.44 (t'), 6.77 (d'), 11.79 (q'), 17.88

(q'), 25.35 (t'), 27.27 (t'), 27.37 (t'), 28.11 (t'), 53.49 (s'), 58.33 (d'), 63.17 (t'), 65.58 (t'), 68.11 (t'), 126.50 (d'), 126.81 (d'), 128.15 (d'), 142.00 (s'), 205.07 (d'); exact mass *m/z* calcd for $C_{32}H_{60}NO_3Si_2$ (M + H) 562.4106, found, 562.4104.

(2*R*,6*R*)-[6-Formyl-1-(phenylmethyl)-6-(2-propenyl)piperidin-2-yl]methyl 2,2-Dimethylpropanoate (62.1).

55.1 **62.1**

Dry DMSO (0.633 g, 0.58 mL, 8.12 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (0.773 g, 0.53 mL, 6.09 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 30 min, and a solution of **55.1** (0.621 g, 1.73 mmol) in CH_2Cl_2 (5 mL plus 2 mL as a rinse) was added dropwise over 20 min. Stirring was continued at -78 °C for 1 h. Et_3N (2.82 mL, 20.3 mmol) was added dropwise over 20 min. Stirring was continued at -78 °C for 1 h, and the cold bath was replaced by an ice bath. The mixture was stirred at 0 °C for 30 min. Hexane (20 mL) was added, and the mixture was filtered through a pad of Celite (3.5 x 2 cm), using Et_2O (2 x 5 mL). Evaporation of the filtrate and flash chromatography of the residue over silica

gel (2.5 x 15 cm), using 2% EtOAc-hexane, gave **62.1** (523 g, 85%) as a colorless, thick oil: FTIR (CH_2Cl_2 cast) 3063, 2956, 2871, 1729 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 9 H), 1.40-1.80 (m, 6 H), 2.47 (dd, *J* = 14.1, 8.6 Hz, 1 H), 2.62 (dd, *J* = 14.1, 6.0 Hz, 1 H), 2.98-3.07 (m, 1 H), 3.65 (dd, *J* = 11.3, 7.3 Hz, 1 J), 3.87 (s, 2 H), 4.09 (dd, *J* = 11.3, 4.4 Hz, 1 H), 5.04-5.18 (m, 1H), 5.82-5.94 (m, 1 H), 7.16-7.23 (m, 1 H), 7.25-7.32 (m, 2 H), 7.36-7.43 (m, 2 H), 9.51 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.58 (t'), 27.13 (q'), 28.09 (t'), 28.38 (t'), 33.12 (t'), 38.65 (s'), 53.76 (t'), 55.58 (d'), 65.65 (t'), 69.63 (s'), 117.98 (t'), 126.79 (d'), 126.82 (d'), 128.33 (d'), 133.64 (d'), 141.22 (s'), 178.05 (s'), 204.04 (d'); exact mass *m/z* calcd for $C_{22}H_{32}NO_3$ (M + H) 358.2377, found, 358.2379.

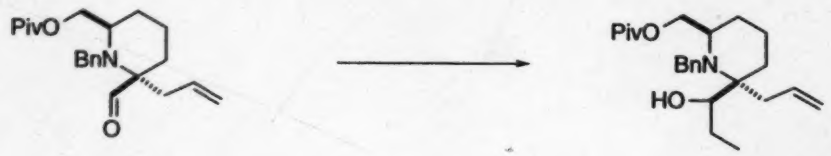
(2*R*,6*R*)-[6-(2-Bromoethenyl)-6-(2-propenyl)-piperidin-2-yl]methyl 2,2-Dimethylpropanoate (62.2).

62.1 **62.2**

$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.27 mL, 0.14 mmol) was added over 5 min to a stirred and cooled (0 °C) solution of (bromomethyl)triphenylphosphonium bromide (55 mg, 0.13 mmol) in THF (10 mL). The ice bath was left in place, but was not recharged. Stirring was continued for 1 h, during which time

the mixture attained room temperature. The mixture was recooled to 0 °C, and a solution of **62.1** (26 mg, 0.073 mmol) in THF (3 mL plus 2 mL as a rinse) was added dropwise over 10 min. The ice bath was left in place, but was not recharged, and stirring was continued for 4 h. MeOH (1 mL) was then added. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.3 x 15 cm), using 2% EtOAc-hexane, gave **62.2** (28 mg, 87%) as a colorless, thick oil, which was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3064, 2934, 2869, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 9 H), 1.46-1.73 (m, 4 H), 1.81-1.89 (m, 1 H), 2.14-2.25 (m, 1 H), 2.56 (dd, J = 14.7, 7.4 Hz, 1 H), 2.80 (dd, J = 14.7, 6.8 Hz, 1 H), 3.20-3.13 (m, 1 H), 3.78 (dd, J = 11.0, 8.0 Hz, 1 H), 3.93 (AB q, J_{AB} = 16.2 Hz, Δ_{AB} = 12.9 Hz, 2 H), 4.10 (dd, J = 11.0, 4.4 Hz, 1 H), 5.00-5.14 (m, 2 H), 5.84-5.98 (m, 1 H), 6.12 (d, J = 8.4 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1 H), 7.14-7.20 (m, 1 H), 7.23-7.31 (m, 2 H), 7.31-7.40 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.14 (t'), 26.48 (t'), 27.22 (q'), 32.42 (t'), 38.69 (s'), 39.07 (t'), 51.37 (t'), 54.78 (d'), 62.88 (s'), 64.09 (t'), 104.52 (d'), 117.30 (t'), 126.33 (d'), 127.15 (d'), 128.08 (d'), 134.47 (d'), 139.02 (d'), 141.81 (s'), 178.13 (s'); exact mass *m/z* calcd for $C_{23}H_{33}BrNO_2$ (M + H) 434.1689, found, 434.1696.

(2*R*,6*R*)-[6-(1-hydroxypropyl)-1-(phenylmethyl)-6-(2-propenyl)piperidin-2-yl]methyl 2,2-Dimethylpropanoate (63.1).

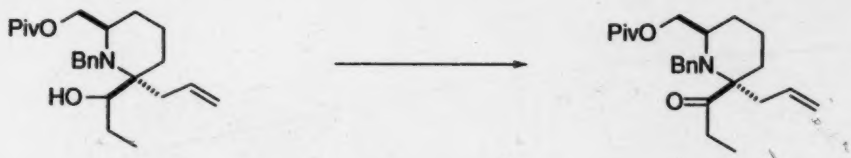


62.1 **63.1**

EtMgBr (1.0 M in Et_2O, 0.90 mL, 0.90 mmol) was added dropwise over 10 min to a stirred and cooled (-78 °C) solution of **62.1** (99 mg, 0.28 mmol) in THF (10 mL). Stirring was continued at -78 °C for 30 min. The cold bath was left in place, but was not recharged, and stirring was continued for 2 h, during which time the mixture attained room temperature. Stirring was continued for an additional 2 h, and saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave **63.1** (60 mg, 56%) as a colorless, thick oil. The relative stereochemistry at the hydroxyl-bearing carbon was not established: FTIR (CH_2Cl_2 cast) 3513, 3069, 3025, 2958, 2935, 2872, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, J = 7.3 Hz, 3 H), 1.12 (s, 9 H), 1.38-1.82 (m, 8 H), 2.15 (s, 1 H), 2.47 (dd, J = 14.8, 7.3 Hz, 1 H), 2.58 (dd, J = 14.8, 7.1 Hz, 1 H), 2.93-3.03 (m, 1 H), 3.45 (d, J = 9.6 Hz, 1 H), 3.74-3.86 (m, 2 H), 4.11

(dd, J = 11.2, 4.3 Hz, 1 H), 4.16 (d, J = 17.0 Hz, 1 H), 4.98-5.14 (m, 2 H), 5.92-6.08 (m, 1 H), 7.13-7.19 (m, 1 H), 7.23-7.29 (m, 2 H), 7.30-7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.09 (q'), 18.13 (t'), 25.74 (t'), 27.23 (q'), 27.43 (t'), 29.47 (t'), 35.13 (t'), 38.13 (s'), 52.46 (t'), 56.83 (d'), 63.06 (s'), 66.49 (t'), 79.75 (d'), 116.98 (t'), 126.32 (d'), 126.83 (d'), 128.23 (d'), 135.94 (d'), 141.81 (s'), 178.06 (s'); exact mass m/z calcd for $C_{24}H_{38}NO_3$ (M + H) 388.2846, found, 388.2843.

[6-(1-Oxopropyl)-6-(2-propenyl)-1-(phenylmethyl)-piperidin-2-yl]methyl 2,2-Dimethylpropanoate (63.2).

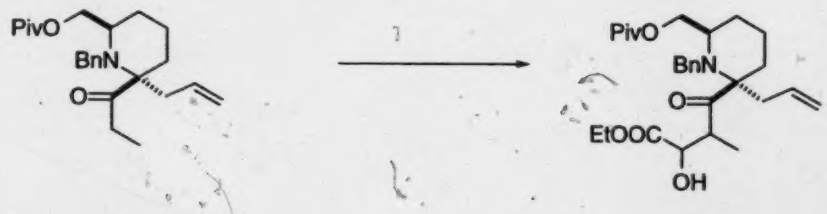


63.1 **63.2**

Dry DMSO (33 mg, 0.030 mL, 0.42 mmol) was added dropwise over 5 min to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (40 mg, 0.028 mL, 0.31 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 30 min and a solution of **63.1** (41 mg, 0.11 mmol) in CH_2Cl_2 (3 mL plus 2 mL as a rinse) was added dropwise over 20 min. Stirring was continued at -78 °C for 1 h. Et_3N (0.15 mL, 1.06 mmol) was added dropwise over 20 min. Stirring was continued at -78 °C for 1 h, and the cold bath was replaced by an ice bath. The mixture was stirred at 0 °C for 30 min. Hexane (20 mL) was added. The mixture was

filtered through a pad of Celite (3.5 x 2 cm), using Et_2O (2 x 5 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 3% EtOAc-hexane, gave **63.2** (34 mg, 84%) as a colorless, thick oil: FTIR (CH_2Cl_2 cast) 3066, 3026, 2971, 2937, 1729, 1707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.3 Hz, 3 H), 1.13 (s, 9 H), 1.44-1.96 (m, 6 H), 2.44-2.74 (m, 4 H), 2.92-3.04 (m, 1 H), 3.64 (dd, J = 11.2, 7.6 Hz, 1 H), 3.82 (q, J = 16.5 Hz, 2 H), 4.98-5.34 (m, 2 H), 5.70-5.85 (m, 1 H), 7.13-7.21 (m, 1 H), 7.22-7.30 (m, 2 H), 7.31-7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 8.30 (q'), 18.23 (t'), 27.21 (q'), 27.86 (t'), 30.05 (t'), 30.36 (t'), 34.52 (t'), 38.70 (s'), 54.05 (t'), 56.37 (d'), 65.67 (t'), 71.07 (s'), 117.40 (t'), 126.41 (d'), 126.64 (d'), 128.11 (d'), 134.49 (d'), 140.99 (s'), 177.89 (s'), 215.00 (s'); exact mass *m/z* calcd for $C_{24}H_{36}NO_3$ (M + H) 386.2690, found, 386.2686.

Ethyl 6-[[(2,2-Dimethyl-1-oxopropyl)oxy]methyl]-4-[1-(phenylmethyl)-2-(2-propenyl)piperidin-2-yl]-2-hydroxy-3-methyl-4-oxobutyrate (63.3).



63.2 **63.3**

BuLi (2.5 M in hexane, 0.055 mL, 0.14 mmol) was added

dropwise over 5 min to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (14 mg, 0.019 mL, 0.14 mmol) in THF (5 mL). Stirring was continued at -78 °C for 20 min and a solution of **63.2** (36 mg. 0.093 mmol) in THF (3 mL plus 2 mL as a rinse) was added over 10 min. Stirring was continued for 1 h at -78 °C and then a solution of EtO_2CCHO (50% in PhMe, 0.037 mL, 38 mg, 0.37 mmol) was added over 5 min. Stirring was continued for 2 h at -78 °C and saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with Et_2O (2 x 10 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2% EtOAc-hexane, gave **63.3** (27 mg, 59%) as a colorless, thick oil: FTIR (CH_2Cl_2 cast) 3491, 3064, 2975, 2871, 1727, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (d, *J* = 7.0 Hz, 1.5 H), 1.00-1.16 (m, 10.5 H), 1.25-1.36 (m, 3 H), 1.46-2.10 (m, 6 H), 2.46-2.72 (m, 2 H), 2.86-3.02 (m, 1 H), 3.12-3.24 (m, 1 H), 3.44-4.40 (m, 8 H), 5.00-5.18 (m, 2 H), 5.66-5.96 (m, 1 H), 7.08-7.40 (m, 5 H); exact mass *m/z* calcd for $C_{28}H_{42}NO_6$ (M + H) 488.3007, found, 488.3004. The ^{13}C NMR is too complicated to be helpful, as the material is a mixture of rotamers of diastereoisomers.

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